APRIL, 1951
VOL. III NO. 4

Circulation

e JOURNAL of the AMERICAN HEART ASSOCIATION

Published by Grune & Stratton, Inc.

"meat without salt is fit only for dogs"

HEBREW PROVERB

When your cardiac or other patients requiring salt restriction find that the flavor of salt is essential to their enjoyment of food, Neocurtasal—sodium-free salt substitute—will give the desired salty tang to otherwise "flat" foods.

Neocurtasal®

Neocurtasal is completely sodium-free. It contains potassium chloride, ammonium chloride, potassium formate, calcium formate, magnesium citrate and starch. Potassium content 36%; chloride 39.3%; calcium 0.3%; magnesium 0.2%.

Available in convenient 2 oz. shakers and 8 oz. bottles.

Write for pad of diet sheets..... Winthrop-Stearns INC.

NEW YORK, N. Y. WINDSOR, ONT.

Circulation
The Journal of the American Heart Association

APRIL 1951
VOL. III NO. 4

Polyarteritis Nodosa

A Correlation of Clinical and Postmortem Findings in Seventeen Cases

By GEORGE C. GRIFFITH, M.D., AND I. LUTFI VURAL, M.D.

The correlation of the clinical and postmortem findings shows that there is no close relationship between the syndrome of polyarteritis nodosa and the allergic states, that pain is the most common symptom, that congestive heart failure is the common cause of death. There is no consistent relationship of the symptomatology referable to the gastrointestinal, central nervous, and pulmonary systems to the pathologic lesions found. Above all, it is to be noted that although hypertension is one of the most frequent signs of polyarteritis, it may develop very late. Therefore, the rejection of this diagnosis because of the absence of hypertension will lead to error, as may the absence of eosinophilia and subcutaneous nodules.

THE GROSS pathologic features of this disease were first described by von Rokitansky[1] in 1852. Fourteen years later Kussmaul and Maier[1a] endeavored to present the microscopic as well as the gross pathology and first used the name periarteritis nodosa. Since that time a good many names have been used for this disease. W. E. Carnegie Dickson[2] distinguished between the true periarteritis nodosa and polyarteritis acuta nodosa. According to this author, true periarteritis nodosa commences in and affects chiefly the outer coat of the diseased vessels and the majority of the instances are due to syphilis. On the other hand, he recognized a rare group of cases which are characterized by the presence of small localized nodules situated upon the walls of the smaller and medium-sized arteries. These nodules are due to localized inflammatory, destructive and proliferative changes occurring in the vessel walls. The most important part of the change probably is complete destruction of localized areas in the muscular coat. The name polyarteritis acuta nodosa, suggested by Ferrari in 1903, should be applied to this latter type of disease. In addition, other authors call this disease necrotizing panarteritis, and some use the name of essential polyarteritis. Because of common usage, in this paper the syndrome will be referred to as polyarteritis nodosa.

Many organisms have been accused as the causative agent of the disease.[3–5] According to some investigators there is good reason to believe that bacterial or other hypersensitivity is responsible for polyarteritis nodosa in many cases.[6,7]

The disease is a destructive "inflammatory-necrotizing" reaction of the vascular tree. The small elastic arteries and arterioles are chiefly affected. The frequency with which various parts of the body are involved was listed by Arkin[8] as follows: kidneys, 80 per cent; heart, 70 per cent; liver, 65 per cent; gastrointestinal tract, 50 per cent; pancreas, 25 per cent; mesenteric artery, 30 per cent; muscles, 30 per cent; peripheral nerves, 20 per cent; and central nervous system, 8 per cent.

Polyarteritis nodosa may occur at any age; 10 days and 77 years are the recorded ex-

From the University of Southern California, School of Medicine, Department of Cardiology; and the Los Angeles County Hospital, Los Angeles, Calif.

tremes. Males predominate in a ratio of at least 3 to 1. The disease is very polymorphic in nature. Almost any symptom may occur.

Purpose and Material

The purpose of this study is to correlate the clinical evidence with the pathologic findings in 17 cases of polyarteritis nodosa. Case studies were taken from the Los Angeles County Hospital and from the Birmingham Veterans' Administration Hospital records. In the review of this syndrome, special consideration and emphasis has been placed on the clinical and pathologic findings in the cardiovascular system. A careful review of the case studies was made and statistical compilations were recorded in order to correlate specific organ lesions with clinical manifestations resulting from both collagenous and noncollagenous diseases.

Between 1939 and 1948 inclusive 16 cases of polyarteritis nodosa were among the 19,242 autopsies performed in the Los Angeles County Hospital. With 1 additional case taken from the files of Birmingham Veterans Administration Hospital this number totals 17. At the Los Angeles County Hospital, where each year an average of 2000 autopsies are performed, no cases were encountered by autopsy surgeons during the years of 1939, 1943 and 1947. The average autopsy incidence of polyarteritis nodosa during this 10 year period was 0.083 per cent. These facts demonstrate well that polyarteritis nodosa is not a common disease.

The patients ranged in age from 30 to 72, the mean age being 51. Fourteen patients (82.3 per cent) were male and 3 (17.6 per cent) were female, a 5 to 1 ratio. Thirteen patients were white and 4 were Negroes, a 3 to 1 ratio.

Clinical Observations

The past history of the cases revealed tonsillitis in 8, syphilis in 3, malaria in 2, bronchial asthma in 1, diabetes in 1, measles, mumps and whooping cough in 1, recurrent exfoliative dermatitis in 1, typhoid fever in 1, toxic delirium in 1, and coronary occlusion in 1 case. Other than tonsillitis, there was no constantly recurring disease in the past history.

Pain was the most common complaint among the patients; it was encountered in 11 instances. It was located only in the abdomen in 3, only in the chest in 2, only in the joints in 1, only in the flanks in 1, in the abdomen and chest in 2, and in the abdomen and extremities in 2 cases. Pain in the extremities and severe headache was the chief complaint of 1 patient.

Shortness of breath occurred in 8, nausea and vomiting in 6, numbness, tingling and weakness in the extremities in 3, one-sided paralysis in 2, wrist-drop in 1, and weight loss in 9 of the cases. Thus pain and shortness of breath were the most common complaints.

In 16 of 17 cases pulse rates were above 100 per minute. Thirteen of 17 had fever at some time during their illness. Of 17 cases 11 had edema. The important signs and symptoms with their frequency are shown in table 1. Tachycardia, fever, and edema were the outstanding signs.

Table 1.—*The Important Symptoms and Signs in Seventeen Cases of Polyarteritis Nodosa*

Signs and Symptoms	Cases	
	Number	Per Cent
Tachycardia	16	94.
Hypertension*	13	81.2
Fever	12	70.5
Pain	11	64.7
Hepatomegaly	11	64.7
Edema	11	64.7
Clinically detectable left ventricular enlargement	9	52.9
Dyspnea	8	47.
Nausea and vomiting	6	35.2
Anorexia	6	35.2
Auricular fibrillation	3	17.6
Apical systolic murmur	3	17.6
Gallop rhythm	2	11.7
Lymphadenopathy	2	11.7
Subcutaneous nodules	2	11.7
Skin rash	2	11.7
Hemiplegia	2	11.7
Diarrhea	2	11.7
Disorientation and mental confusion	2	11.7
Foot-drop	1	5.8
Wrist-drop	1	5.8
Total aphasia	1	5.8
Right hemianopsia	1	5.8
Melena	1	5.8

* Blood pressures were recorded in 16 cases.

The shortest duration of the condition from the beginning of the first symptoms was one month and the longest seven years, the average duration being eight and twelve months. The reported causes of death were as follows: congestive heart failure in 6; renal insufficiency in 5; bronchopneumonia in 3; toxemia and ca-

chexia in 1; liver abscess resulting from secondary infection of polyarteritic infarctions and generalized peritonitis in 1; gangrene of feet and hand in 1. The causes of death were directly attributable to the lesions of polyarteritis nodosa.

Cardiovascular System

Clinical Data. Chest pain was among the chief complaints in 3 of the patients. In 2 it was located in the precordium, and in 1 under the right nipple. Eight of the 17 patients complained of shortness of breath but this symptom occurred rather late.

Of the 16 cases in which blood pressure measurements were recorded 13 showed a diastolic pressure of more than 90 mm. Hg and the highest reading was 208/130.

Nine of the 17 cases had a clinically detectable left ventricular enlargement. Apical systolic murmurs were present in 3, gallop rhythm in 2 and auricular fibrillation in 3.

Electrocardiograms were taken in 11 cases. Ten showed some type of abnormality, axis deviation being present in 6, and T-wave changes in 4 of the 11 cases. In case 17 the electrocardiogram revealed right axis deviation and electrical alternans, and in case 7 it showed auricular fibrillation and right bundle branch block (table 2).

Congestive heart failure with hepatomegaly and edema constituted terminal findings and was considered the cause of death in 6 cases. One patient developed gangrene of the feet, bilaterally, and of the left hand, and died of secondary bronchopneumonia.

Pathologic Data. In 13 of the 17 cases studied there was some pathologic abnormality in the heart. In 10 of these, there was left ventricular hypertrophy and the largest heart weighed 910 Gm. Three cases had myocardial infarction in the anterior portion of the left ventricular wall, and 3 others had diffuse scarring of the myocardium. Nine cases showed slight to moderate degree of coronary atherosclerosis.

In 7 cases (43.7 per cent) there was evidence of polyarteritis nodosa in the heart; in 5, in the large coronary arteries; in 2 the small vessels of the myocardium were involved. One of 3 myocardial infarctions was very recent, and the typical changes of polyarteritis nodosa were present in the large and small coronary arteries. The other infarctions were due to causes unrelated to polyarteritis nodosa. In 1 case, the distal one-third of the main coronary arteries was covered with many tiny, white nodules measuring 1 to 2 mm. in diameter which in some areas completely occluded the lumen. These nodules were also present throughout the myocardium and the latter revealed multiple areas of fibrosis. In 3 other

Table 2.—*Electrocardiographic Changes Seen in Ten of Seventeen Cases of Polyarteritis Nodosa*

Case Number	Electrocardiographic Changes
1	Sinus tachycardia Low voltage Left axis deviation
2	Sinus tachycardia Low voltage Trigeminy Isoelectric T_1, T_2, T_3 Deep Q_1, and Q_{IVF}
3	Sinus tachycardia Left axis deviation Isoelectric T_1, flat T_2 and T_3
6	Left axis deviation Auricular fibrillation
7	Low voltage Auricular fibrillation Right bundle branch block
8	Sinus tachycardia Prolonged Q-T interval Isoelectric T_1, flat T_2 and T_3
9	Sinus tachycardia Flat T_1, inverted T_2 and T_3 of coronary type
11	Simple sinus tachycardia
12	Auricular fibrillation Left axis deviation Old anterior myocardial infarction
15	Sinus tachycardia Right axis deviation Electrical alternans

cases in which the vascular lesions of polyarteritis nodosa were found in the coronary arteries, the myocardium showed diffuse fibrosis. Two others revealed scarring and round cell infiltration around the vessels in the myocardium.

Of 7 cases with polyarteritic changes in the heart, clear, yellow pericardial fluid was present in 3, in the amount of 20, 30, and 66 cc. respectively. In another case a thick coat of yellow fibrin united the visceral and parietal pericardium. In still another case the pericardium was shaggy and was covered with white, fibrous tissue.

Correlation of Clinical and Pathologic Findings. In 1 of the 3 cases in which chest pain was present, vascular changes of polyarteritis nodosa occurred in the small vessels of the myocardium. In 2 other cases chest pain was unrelated to polyarteritis nodosa, pain in 1 being due to pulmonary infarction in the right lower lobe from emboli originating in the heart, and in the other being the result of coronary atherosclerosis with myocardial infarction.

In all of the 13 cases in which hypertension was present there were vascular changes of polyarteritis nodosa in the kidneys. Conversely, hypertension developed in 13 of 14 cases showing vascular lesions of polyarteritis nodosa in the smaller arteries of the kidney. The remaining patient had multiple infarcts and yet had a normal blood pressure. This latter patient, however, was in a cachectic state.

Six of 11 cases in which an electrocardiographic left axis deviation was present showed left ventricular hypertrophy at necropsy. Of 7 cases in which hearts showed vascular lesions of polyarteritis nodosa, electrocardiograms were taken in 5. Of these, case 1 had a low voltage and left axis deviation; necropsy showed polyarteritis nodosa in the coronary arteries and diffuse scarring of the myocardium. Low voltage, in this case, may be very well explained by diffuse scarring of the myocardium. Case 3 had left axis deviation, isoelectric T_1, flat T_2 and T_3. Necropsy revealed marked left ventricular hypertrophy and the vascular changes of polyarteritis nodosa in the small coronary vessels and multiple scars in the myocardium. T-wave changes in this can be explained by myocardial ischemia due to coronary lesions. Case 7 had low voltage, auricular fibrillation and right bundle branch block; autopsy disclosed polyarteritis nodosa in the coronary vessels, a few small pinpoint hemorrhagic areas and small scars about the small vessels, and numerous round cell infiltrations in the myocardium. There was no other pathologic finding to account for the auricular fibrillation; the left auricle was normal in size; the thyroid gland was normal; and the arteries had only minimal sclerosis. Case 9 had flat T_1 and inverted T_2 and T_3 of coronary type. At autopsy the distal one-third of the coronary arteries was covered with many white nodules which in some areas completely occluded the lumen. The myocardium showed multiple areas of fibrosis; the left ventricle was hypertrophied; and the pericardium was shaggy and covered with white fibrous tissue. No infarction was found. Myocardial ischemia due to coronary artery involvement with polyarteritis nodosa and narrowing of the lumen could account for the inverted T waves in this case. Case 17 had right axis deviation and electrical alternans. The positive autopsy findings in the heart of this case were as follows: there was moderately severe dilatation of the right ventricle and right auricle and mild dilatation of the left ventricle and left auricle. Over the surface of the heart, along the course of the smaller blood vessels there were felt several scattered hard nodules measuring 1 to 2 mm. in diameter. At the apex of the right ventricle, one nodule measured 2 to 4 mm. and cut section revealed it to consist of dense, thick, white tissue which was not encapsulated. There were a few areas of slightly increased firmness due to apparent scarring. The endocardium showed a few tiny areas of petechial hemorrhages. The microscopic examination of the myocardium revealed on one section mild edema of epicardium with moderate round-cell infiltration about small epicardial vessels, moderate thickening of walls of small muscular arteries of heart. Another section appeared fairly normal except for arteriolar thickening and small patchy areas of interstitial fibrosis. Sections through several small epicardial coronary arteries of muscular type showed eccentric perivascular focal scar-

ring with only a very few residual round cells. This lesion was characteristic in other sections of the myocardium, where extensive scarring had occurred, with replacement of muscle tissue by hyalinized fibrous tissue. Lumens of many vessels were markedly narrowed by eccentric foci of fibrous tissue which replaced a segment of the vessel wall, especially the media and inner adventitia. One section showed extensive hyaline scarring with many old thromboses and recanalization of small muscular ar-

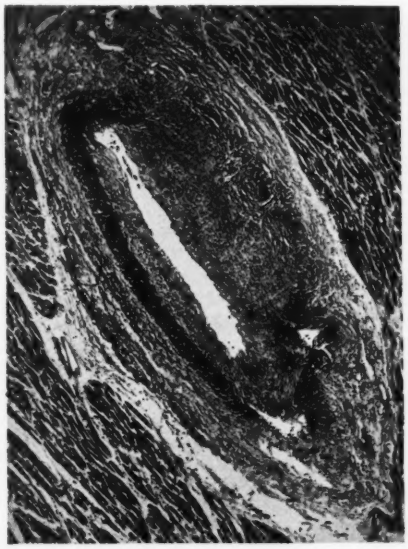


FIG. 1. Case 17, the vascular lesions of polyarteritis nodosa in the coronary artery.

teries. There were relatively few acute lesions, and these were about very small arteries. For the most part, the myocardial lesions represented fairly advanced stages of healing of polyarteritis nodosa (fig. 1). In this case, electrical alternans can be explained by diffuse myocardial scarring which was apparently caused by the vascular lesions of polyarteritis nodosa in the coronary arteries and in the myocardium. On comparison of the group of 7 cases in which the lesions of polyarteritis nodosa was present in the heart with the group in which it was not present, some differences could be demonstrated. The average age of the patients who had the vascular lesions of polyarteritis nodosa in the heart was 47.5 years; those who did not have the lesions averaged 53.9 years. There were 5 males and 2 females in the group in which cardiac involvement developed, and 9 males and 1 female in the group in which it did not. The average duration of polyarteritis nodosa from the onset of symptoms until death averaged 27 months among patients who had involvement of the heart and 11.3 among those who did not have it. There was no significant difference between the two groups in the level of frequency of hypertension, fever, leukocytosis or other laboratory findings.

URINARY SYSTEM

Clinical Data. One of 17 cases had pain in the flanks. In 14 patients urinalysis showed abnormal findings. All of these 14 cases, at some time while under observation, showed albuminuria. Three of 14 cases showed albuminuria without other clinical evidence of renal disease; 2 had albumin and hyaline and granular casts in the urine, and 4 cases showed albuminuria, leukocyturia and hematuria. Albumin, leukocytes, erythrocytes and casts were found collectively in the urines of 4 out of 14 cases. One case showed albumin, leukocytes, sugar and acetone in the urinalysis. Of 17 patients, 3 showed no abnormality in the urinalysis at any time while under observation.

Of the 9 cases in which nonprotein nitrogen determinations were done, 4 showed values of more than the normal of 40 mg. per 100 cc. of blood, and in one of these, nonprotein nitrogen reached 212 mg. per 100 cc. of blood. In most instances azotemia was terminal in the course of the disease. In 1 of 17 cases the premortem clinical diagnosis was "probable pyonephrosis," in 1, "chronic glomerulonephritis," in another, "uremia."

Pathologic Data. In 14 of the 17 cases studied there was evidence of polyarteritis nodosa in the kidneys. The vascular changes of polyarteritis nodosa were found in all sizes of arteries from the renal arteries to arterioles and occasionally in veins. The degree of involvement of arteries varied markedly; in many cases the process was so extensive that almost all vessels examined were involved, while in a few cases it required careful search to find

arteries with characteristic lesions. In most cases all stages of polyarteritis nodosa were present in the same patient. Figure 2 shows exudative glomerular lesions associated with the acute inflammatory stage of polyarteritis nodosa in the renal arteries and healing with formation of fibrous tissue which in some places encroaches upon the vessel lumen. Infarcts of the kidneys were found in 7 cases. In one case the renal vessels were ruptured and a retroperitoneal hematoma had formed. Seven cases observed at necropsy, there were abnormal urinary findings. Of the 4 cases with retention of nonprotein nitrogen of more than the normal, 40 mg. per 100 cc. of blood, 1 showed no vascular lesions of polyarteritis nodosa in the kidneys. All cases of glomerulonephritis were associated with polyarteritis nodosa of the renal vessels and 6 of 7 showed abnormal urinary findings. Three of the 14 cases with periarteritic changes in the kidney vessels showed normal urinary findings. In all of these 3 cases, however, only the small vessels of the kidneys were involved and there were no abnormal pathologic findings in the glomerular tufts. In the case complaining of pain in both flanks, autopsy disclosed several large areas of infarction of the kidneys with an infiltration of polymorphonuclear leukocytes in the infarcted areas. Also there was infiltration of the vessel walls in all coats, with round and polymorphonuclear cells. In the left kidney, one of the vessels had ruptured through the anterior surface of the lower pole and caused a large, retroperitoneal hematoma. In the case in which the urinalysis had shown massive leukocyturia with slight

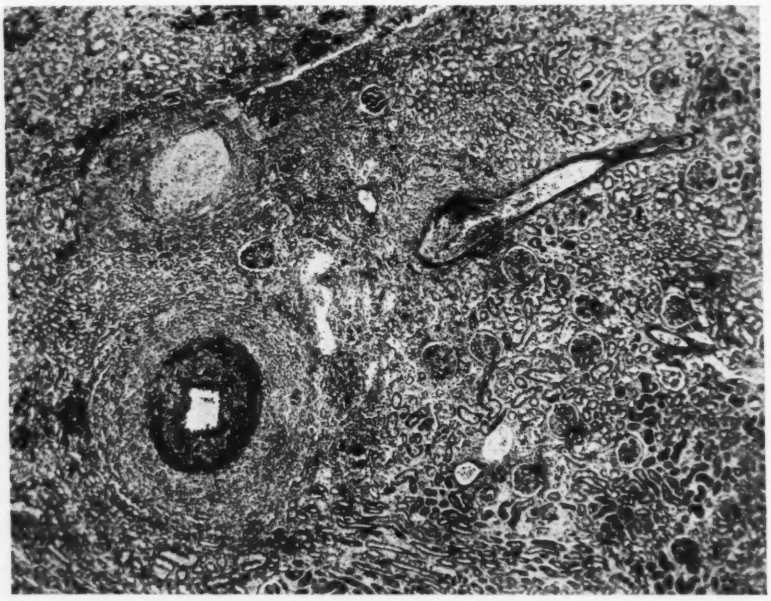


FIG. 2. Case 17, exudative glomerular lesions associated with healing stage of polyarteritis nodosa in the renal arteries.

of glomerulonephritis were found, 3 being necrotizing glomerulonephritis, 3 diffuse chronic glomerulonephritis, 3 diffuse chronic glomerulonephritis, and 1 subacute glomerulonephritis. All of these were the cases in which the vascular lesions of polyarteritis nodosa were present in the kidneys. One case showed numerous miliary abscesses throughout the kidney.

Correlation of Clinical and Pathologic Findings. In 11 of the 14 cases in which abnormal urinary findings were present, there were vascular lesions of polyarteritis nodosa in the kidneys. Conversely, in all of 14 cases in which vascular changes of polyarteritis nodosa were

hematuria and moderate albuminuria, and in which a premortem diagnosis of "probable pyonephrosis" was made, autopsy revealed vascular changes of polyarteritis nodosa in many large arteries and small arteries and numerous miliary abscesses throughout both kidneys. In 5 cases the cause of death was renal in origin.

Gastrointestinal System

Clinical Data. In 10 of the 17 cases, the disease caused symptoms that were referable to the gastrointestinal tract. Abdominal pain occurred in 7 cases. Of these 7 patients 3 had pain only in the abdomen, 2 in the abdomen and in the chest, and 2 in the abdomen and in the extremities. Pain was located anywhere in the abdomen. In this group of cases, the abdominal pain most frequently was located in the right upper quadrant, in the epigastrium or was generalized. One case had undergone a cholecystectomy because of abdominal pain simulating cholecystitis, but the operation failed to relieve the complaints. Weight loss occurred in 9 cases; it was between 10 to 90 pounds during the course of the illness. Nausea and vomiting occurred in 6 of the cases. Of 17 cases, 6 had intractable anorexia and all of these 6 cases had considerable weight loss. Diarrhea occurred in 2 patients. Melena occurred in one patient. Hepatomegaly was present in 11 cases and the livers were found to be enlarged 1 to 3 fingerbreadths below the right costal margin. Spleens were palpable only in 3 cases.

Pathologic Data. In 82.3 per cent of the 17 cases necropsy disclosed typical lesions of polyarteritis nodosa in the gastrointestinal tract. The most commonly affected organ was the liver, there being involvement in 11 cases. The vascular lesions were marked about the hepatic arteries, and all stages including fibrosis and scarring were seen. Thromboses and areas of necrosis were also present in some cases. In case 16 an infarct of the liver due to polyarteritis nodosa was secondarily infected and a resulting abscess had ruptured into the peritoneal cavity. In 6 cases livers revealed passive congestion. The pancreas was involved in 8 cases. The spleen showed the lesions of polyarteritis nodosa in 3 cases. In 12 cases the spleens weighed between 150 and 200 Gm., and in the other five, between 250 and 600 Gm. Perisplenitis, infarctions, hemorrhages, necrosis, and round cell infiltration around the small arteries were among the pathologic findings in the spleen. In 3 cases the vascular changes of polyarteritis nodosa were found in the vessels of mesentery. In 2 other cases the small arteries of the small intestines were involved with polyarteritis nodosa. In one case, the blood vessels in the mesentery and those supplying the entire gastrointestinal tract revealed many tiny, white, firm nodules measuring from 1 to 2 mm. in diameter. The vessels in between these nodules appeared white and some of them slightly thickened.

Correlation of the Clinical and Pathologic Findings. In all of the cases in which abdominal pain occurred, necropsy disclosed the changes of polyarteritis nodosa in the abdominal organs. These pathologic changes were located as follows: in 1 case in the mesentery; in 1 case in the liver and mesentery; in 1 case in the liver, pancreas, and spleen; in 1 case in the liver, pancreas, small intestines; in 2 cases in the gall bladder and liver; in 1 case in the small intestines. Conversely, in 7 of the 17 cases in which lesions of polyarteritis nodosa were observed in the abdominal organs at necropsy, there were no abdominal pains. In all of 6 cases which had nausea and vomiting, necropsy disclosed the changes of polyarteritis nodosa in the viscera as follows: 2 in the mesentery; 1 in the liver and pancreas; 1 in the liver; 1 in the liver, pancreas, spleen and mesentery. One patient who had melena showed at autopsy the changes of polyarteritis nodosa in the vessels of small intestines with some areas of necrosis in the intestinal wall. It was evident that the melena in this patient was caused by small infarctions in the intestinal wall due to polyarteritis nodosa in the vessels. Of 8 cases in which the pancreas was involved by the lesions of polyarteritis nodosa, 1 showed glycosuria and acetonuria. This patient had not had any history of diabetes in the past. In 1 of the 2 cases which had diarrhea, stool cultures revealed paratyphoid A, and in the other diarrhea was apparently due to toxic effect of polyarteritis nodosa on the intestines, because

no lesions of polyarteritis nodosa were found in the intestines, nor could any other cause be demonstrated.

Nervous System

Clinical Data. In 5 of 17 cases, symptoms that were referable to the central nervous system were present. One of these cases showed the symptoms and signs of toxic delirium, 1 right-sided paralysis, 1 left-sided paralysis, and 2 mental confusion.

Of the 17 cases 3 had numbness, tingling and weakness in the extremities, 1 had foot-drop, 1 had wrist-drop, 1 had partial paralysis of the right arm, and 1 had numbness of the feet and hands. The diagnoses of mononeuritis multiplex in 1 and polyneuritis in 3 cases were made clinically.

Pathologic Data. In 9 cases the central nervous system was examined pathologically. Four of the 9 showed the vascular lesions of polyarteritis nodosa in the cerebral vessels. One showed severe atherosclerosis of the cerebral vessels. In 3 cases the examination of the brain revealed normal findings.

Of 9 cases in which the microscopic examination of the peripheral nerves was performed, 5 showed involvement with polyarteritis nodosa. In all of these, the lesions were found in the nutrient arteries and were widespread. The lesions in the nutrient arteries of the nerves were quite similar to those caused by polyarteritis nodosa in the other arteries of the body.

Correlation of Clinical and Pathologic Findings. Of 5 cases in which the clinical signs and symptoms were referable to the central nervous system, 4 revealed at necropsy the characteristic changes of polyarteritis nodosa in the cerebral vessels. One of these cases was admitted to the contagious diseases service because of severe headache and stiffness in the neck; spinal tap showed a bloody fluid. This patient later developed total aphasia, right hemianopsia and flaccid right hemiplegia. At necropsy, the changes of polyarteritis nodosa were found involving the vessels, not only of the circle of Willis, but also of the cerebral cortex and subcortex. It seems quite reasonable to assume that in this case the clinical signs and symptoms of subarachnoid and intercerebral hemorrhage were caused by polyarteritis nodosa of the central nervous system. In 2 cases which showed the clinical picture of psychosis, mental confusion and delirium, the cerebral arteries revealed the typical changes of polyarteritis nodosa. The clinical symptoms were apparently due to cerebral ischemia resulting from the lesions of polyarteritis nodosa of the cerebral vessels. In one case, the hemiplegia was due to severe cerebral atherosclerosis and was not related to polyarteritis nodosa.

Of 7 cases which had clinical symptoms referable to peripheral nerves, 5 showed the vascular changes of polyarteritis nodosa in the nutrient vessels. In one case with the clinical picture of mononeuritis multiplex necropsy revealed the vascular lesions of polyarteritis nodosa in the cerebral vessels. Apparently the clinical picture of mononeuritis multiplex was caused by the toxic effect of polyarteritis nodosa on the peripheral nerves without structural involvement.

Respiratory System

Clinical Data. Dyspnea occurred in 9, chest pain in 3, and cough in 3 of 17 cases. The clinical diagnoses of bronchopneumonia in 4, pneumonia in 3, and possible pulmonary infarction in 1 was entertained.

Pathologic Data. Only 1 of the 17 cases revealed the vascular changes of polyarteritis nodosa in the pulmonary vessels. Arteriosclerosis of the pulmonary arteries was found in one case. Bronchopneumonia was encountered in 3, bronchiectasis in 1, old healed apical tuberculosis in 1, lobar pneumonia in 1, and abdominal emboli in 1.

Correlation of Clinical and Pathologic Data. The correlation of dyspnea with pathologic findings revealed that it was due either to congestive heart failure or to secondary pulmonary inflammation and not to the vascular lesions of polyarteritis nodosa in the lungs. In 1 of 4 patients in whom chest pain was located under the right nipple autopsy disclosed pulmonary emboli originating from the heart. In the case in which the lesions of polyarteritis nodosa were present in the arterioles of the right lung there was an extensive bronchopneumonia.

Skin Lesions

Subcutaneous nodules were found in 2 of 17 cases. In one case, they were located in the upper extremities, on the chest and in the forehead; in the other, only in the upper extremities. Two cases had had skin rashes. In one of these they consisted of blotchy, erythematous patches on anterior thigh and lower legs; in the other, of recurrent exfoliative dermatitis. The latter one was also affected with frontal and parietal alopecia.

Laboratory Findings

Fourteen patients had a hypochromic anemia. In one case the erythrocytic count was as low as 1,870,000 per cu. mm. There was nothing found as a cause for this and a diagnosis of "severe anemia of unknown origin" was made. The patient died of congestive heart failure and autopsy revealed polyarteritis nodosa in the myocardium, in the liver, and in the spleen. There were some hemorrhages in the spleen; this could not be accounted for by the severe anemia. The anemia in this case was probably the result of toxic depression of bone marrow, since the leukocyte and thrombocyte counts also were very low.

Leukocyte counts were done in 16 cases. Thirteen of these 16 had leukocyte counts above 10,000, the highest being 44,000. Three had normal counts. In one patient, the one with severe anemia, the leukocyte count was at the onset 12,200, but toward the end of the disease it dropped to 3,000 per cu. mm. Differential counts showed polymorphonuclear leukocytosis above 80 per cent in 10 of 16 cases in which this procedure was performed. Only one patient showed eosinophilia of 68 per cent; this patient had a history of bronchial asthma for years.

Erythrocytic sedimentation rate was determined in 6 of the cases. All had a rapid sedimentation rate of between 20 and 48 mm. in the first hour.

Two patients had a positive Wassermann reaction in the serum, but it was negative in the cerebrospinal fluid. One patient had a positive Kahn reaction in the serum and negative Wassermann. At autopsy none showed changes of syphilis.

The albumin-globulin ratio was determined in 10 of the cases. Four of these had a total serum protein below 5 Gm., 6 had a normal total serum protein. In 9, the globulin content of the serum was above 2.5 Gm. and in 1 patient it was below this amount.

Comment and Summary

In a study of the clinical and pathologic findings in 17 cases of polyarteritis nodosa confirmed at necropsy, it has been observed that polyarteritis nodosa is more common among males, between the ages of 40 and 50, than among females. Caucasians predominate over Negroes.

Our studies do not confirm the opinion of others[6, 7, 9] that since the entrance of the sulfonamides into the field of therapeutics the number of cases of polyarteritis nodosa has been increased. We also failed to find a close etiologic relationship between allergy and polyarteritis nodosa. Eosinophilia, which has been considered by some authors to be one of the most significant laboratory findings, occurred in only 1 of 17 cases studied, and this patient had a history of bronchial asthma for many years. We are inclined to agree with the view stated by Zeek, Smith and Weeter[10] that polyarteritis nodosa and hypersensitivity angiitis are two different conditions and that it is the latter which is characterized by allergic manifestations, including eosinophilia. But our cases were not studied microscopically from that angle. Subcutaneous nodules also were one of the infrequent signs of the disease.

Pain is the most common symptom, being found in 64.7 per cent of the cases. This finding confirms the idea of French authors that "polyarteritis nodosa is a painful disease." In accordance with the literature this study shows that chest pain is uncommon in polyarteritis nodosa, but may occur. In only one case it was apparently due to the involvement of small vessels in the myocardium by the lesions of polyarteritis nodosa. Shortness of breath is a late symptom in the course of the disease and is due either to heart failure or nonspecific pulmonary complications.

In all of our cases there has been found no consistent correlation between the clinical find-

ings referable to the cardiovascular system and specific types of pathologic changes in the organs of this system. In spite of the fact that hypertension is one of the most common signs of polyarteritis nodosa, it may develop very late and the rejection of the diagnosis of polyarteritis nodosa because of the absence of hypertension is wrong, as it is wrong to reject this diagnosis in the absence of eosinophilia or subcutaneous nodules. The changes in the electrocardiogram were not specific and were due to myocardial ischemia and scarring. Electrical alternans accompanied by vascular lesions of polyarteritis nodosa in the coronary arteries was found in one of the cases studied and is believed to be the first of its kind to be reported in the literature.

There has also been found no consistent correlation between the clinical evidence of renal damage and specific types of pathologic changes in the kidneys. The frequent association of glomerulonephritis and polyarteritis nodosa reported in the literature previously is confirmed.[11–14] This study shows that hypertension in this condition is always associated with arteriolar changes in the kidneys. In all of the 13 cases with hypertension pathologic renal lesions were demonstrated.

The involvement of the gastrointestinal system was very common in polyarteritis nodosa. The lesions were distributed throughout the viscera. Symptoms referable to the gastrointestinal tract were present in 58.7 per cent of the 17 cases. Abdominal pain and nausea and vomiting were the most frequent symptoms. The most commonly involved organ in the abdomen was the liver. Splenomegaly was found only in a small percentage of the cases.

The central nervous system was examined microscopically in 9 cases. Four of these showed characteristic changes in the cerebral vessels. In the authors' opinion the involvement of the central nervous system in polyarteritis nodosa is not rare; with careful examination the percentages reported in the literature will increase more and more.[17]

According to this study the pulmonary involvement in polyarteritis nodosa is rare as it was observed only in one case. This is in conflict with the findings of some investigators,[15, 16] but in accord with the findings of Barnard and Burbury,[18] Lichtman, Stickney and Kernohan,[19] and Herburt and Price.[20]

REFERENCES

[1] Von Rokitansky, C.: Denkschr. d. k. Akad. d. Wessensch. **4:** 49, 1852.

[1a] Kussmaul, A., and Maier, R.: Über eine bisher nicht beschriebene eigentumliche Arterienerkrankung (Periarteritis nodosa) die mit Morbus Brightii and rapid fortschreitender allgemeiner Muskellähmung einhergeht. Deutches Arch. f. klin. Med. **1:** 484, 1866.

[2] Dickson, W. E. C.: Polyarteritis acuta nodosa and periarteritis nodosa. J. Path. & Bact. **12:** 31, 1907.

[3] Friedberg, C. K., and Gross, L.: Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease with a note on abdominal rheumatism. Arch. Int. Med. **54:** 170, 1934.

[4] Chvostek, and Weichselbaum, A.: Herdweise syphilitische Endarteritis mit multipler Aneurysmenbildung. Allg. Wien. med. Ztng. **22:** 257, 1877.

[5] Reimann, H. A., Price, A. H., and Herburt, P. A.: Trichiniasis and periarteritis nodosa. J.A.M.A. **122:** 274, 1943.

[6] Rich, A.: The role of hypersensitivity in periarteritis nodosa, as indicated by seven cases developing during serum sickness and sulfonamide therapy. Bull. Johns Hopkins Hosp. **71:** 123, 1942.

[7] —, and Gregory, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. Bull. Johns Hopkins Hosp. **72:** 56, 1943.

[8] Arkin, A.: A clinical and pathological study of periarteritis nodosa: a report of five cases, one histologically healed. Am. J. Path. **6:** 401, 1930.

[9] Rich, A. R.: Hypersensitivity to iodine as cause of periarteritis nodosa. Bull. Johns Hopkins Hosp. **77:** 43, 1945.

[10] Zeek, P., Smith, C., and Wester, J. C.: Studies on periarteritis nodosa: the differentiation of periarteritis nodosa and of hypersensitivity. Am. J. Path. **24:** 889, 1948.

[11] Ralston, D. E., and Kvale, W. F.: The renal lesions of periarteritis nodosa. Proc. Staff Meet., Mayo Clin. **24:** 18, 1949.

[12] Rolnick, R. C., and Davidsohn, I: Involvement of the kidney in periarteritis nodosa. Urol. & Cutan. Rev. **96:** 626, 1942.

[13] Boyd, L. J.: The renal and cardiac manifestations of periarteritis nodosa. Bull. New York M Coll., Flower & Fifth Ave. Hosps. **4:** 176, 1941.

[14] Ehrstrom, M. D.: Irreversible allergic reactions with nonbacterial antigen, glomerulonephritis,

periarteritis nodosa, rheumatic fever, arteritis, etc. Acta med. Scandinav. **9:** 346, 1938.

[15] HARKAVEY, J.: Vascular allergy; pathogenesis of bronchial asthma with recurrent pulmonary infiltrations and eosinophilic polyserositis. Arch. Int. Med. **67:** 709, 734, 1941.

[16] HARRIS, A. W., LYNCH, G. W., AND O'HARE, J: Periarteritis nodosa. Arch. Int. Med. **63:** 1163, 1939.

[17] KERNOHAN, J. W., AND WOLTMAN, H. W.: Periarteritis nodosa. Arch. Neurol. & Psychiat. **39:** 655, 1938.

[18] BARNARD, W. G., AND BURBURY, W. M.: Gangrene of the fingers and toes in a case of polyarteritis nodosa. J. Path. & Bact. **39:** 285, 1934.

[19] LICHTMAN, A. L., STICKNEY, J. M., AND KERNOHAN, J. W.: Periarteritis nodosa. Report of a case. Proc. Staff Meet., Mayo Clin. **18:** 500, 1943.

[20] HERBURT, P. A., AND PRICE, A. H.: Periarteritis nodosa producing aneurysm of renal artery and hypertension. Arch. Path. **39:** 274, 1945.

Acute and Subacute Disseminated Lupus Erythematosus

A Correlation of Clinical and Postmortem Findings in Eighteen Cases

By GEORGE C. GRIFFITH, M.D., AND I. LUTFI VURAL, M.D.

Eighteen cases of disseminated lupus erythematosus were verified by postmortem study in a series of 19,242 autopsies. Shortness of breath was the most common complaint and occurred in 16. Fourteen of this number had definite cardiac pathology. All 16 had definite pulmonary pathology. Fourteen cases had abnormal urinalysis. Of these cases, 7 had elevated blood nonprotein nitrogen values of over 40 mg., and only 4 had hypertension. However, 14 cases had abnormal pathologic renal findings. Fifteen of the 18 cases had a skin lesion; 11 of the 15 were definitely of the lupus type. Hypochromic anemia was present in 17, leukopenia in 14, elevated sedimentation rate in all cases recorded and an elevated serum globulin in 9. The diagnosis is made by summation of the clinical findings; namely, shortness of breath, joint pains, skin rash, fever, pulmonary, cardiac, and renal abnormalities, and by the laboratory findings of hypochromic anemia, albuminuria, increased sedimentation rate, elevated serum albumin, presence of lupus erythematosus cells, and by a positive skin biopsy.

LUPUS erythematosus was first described by Hebra as a cutaneous disease and was named "seborrhea congestiva," in 1845. Six years later Cazenave gave the disease its present name becaue he thought that it was an erythematous form of "lupus" which later was considered as a form of cutaneous tuberculosis. In 1872 Kaposi pointed out that the disease sometimes had systemic reactions and was at times fatal. The clinical features of the disease were clarified by Jadassohn and later by Osler. In 1924 Libman and Sacks[1] described a nonbacterial verrucous endocarditis which involved the cardiac valves and the mural endocardium. Subsequent studies have shown that vascular lesions involving vascular endothelium and subendothelial tissue and similar lesions of the serous membranes were common in the latter condition and in lupus erythematosus. According to Baehr, Klemperer and Schifrin,[2] in both diseases typical changes in the blood vessels were widely disseminated throughout the body. Guion and Adams[3] concluded that disseminated lupus erythematosus is primarily a diffuse vascular disease affecting chiefly small arteries and arterioles. Klemperer[4] believes that acute lupus erythematosus is a disease characterized by a fundamental alteration of the collagen portion of the connective tissue.

Today most investigators agree that lupus erythematosus has no connection with the tubercle bacillus. The real etiology of the disease is unknown. Some British authors have become convinced that hemolytic streptococci are responsible for the disease.[5] Others[6–8] have claimed allergy to be the cause. However, Baehr and Pollack[9] are opposed to this idea.

The fundamental pathologic process takes place in the connective tissue. All elements of this tissue are injured. The vascular changes are similar no matter where they occur. The edema and fibrinoid degeneration in the subendothelium is followed by endothelial proliferation leading ultimately to thrombosis. There are frequently collections of lymphocytes and fibroblasts in and around the adventitia and in the media. The heart is frequently enlarged. Atypical verrucous endocarditis is now thought to be a local variant of the disease. Fibrinoid degeneration may also affect the mural endocardium with the formation of small vegetations. The mitral valve is most commonly affected.

From the University of Southern California, School of Medicine, Department of Cardiology; and the Los Angeles County Hospital, Los Angeles, Calif.

The valves are richly vascularized. In addition, the myocardium often shows foci of segmented leukocytes but Aschoff bodies have not been described. The cardiac lesions were analyzed by Humphreys.[10] Twelve cases had endocardial lesions and most of the cases showed some focal myocarditis. In 9 cases a serofibrinous pericarditis was present. In this condition the spleen reveals a peculiar periarterial fibrosis confined to the central and pericillary arteries, which was first described by Libman and Sacks. In microscopic examination, a thick collar of connective tissue is seen around the central arteries and resembles "onion skin." According to Teilum,[8] the hyperglobulinemia and periarterial fibrosis occurring in the spleen in lupus erythematosus are identical pathogenetically and morphologically with the alteration in Boeck's sarcoid and the atypical amyloidosis, having allergic hyperglobulinosis as the common primary foundation. Another lesion of frequent occurrence is the special alteration of the glomerular coils of the kidneys which has been characterized as "wire loops" by Baehr, Klemperer and Schifrin[2] because of the resemblance of the coils to bent wire. According to Klemperer, Pollack and Baehr,[4,9] the coils are irregularly thickened and rigid, and strongly eosinophilic. In other cases, there is focal fibrinoid necrosis of part of the glomerular coils, the others remaining unaffected.

The disease is most common in the third decade of life. However, patients under the age of 30 years have been reported in the literature.[11] Less than 5 per cent of the cases are males. Dermatologists[12] recognize four types of lupus erythematosus: (1) the localized or chronic discoid type, (2) the generalized discoid type, (3) the subacute disseminated type, and (4) the acute disseminated type. The discoid type is not associated with visceral vascular and endothelial lesions. The course of subacute type is characterized by intermissions between exacerbations. During these intermissions the patient has no symptoms. On the other hand, the acute type has no interruption at all, or, if any, only incomplete and short-lasting. The clinical manifestations in acute disseminated lupus, with their frequency, have been listed as follows by Montgomery[13]: fever, in 97 per cent; anemia, in 84 per cent; leukopenia (less than 4,000), in 71 per cent; arthralgia or arthritis, in 63 per cent; and albuminuria, cylindruria and microscopic hematuria, in 32 per cent of the cases. One of the most constant signs is fever. It may be accompanied by chills and profuse sweats. Tachycardia is proportional to the degree of temperature. The cutaneous lesions are merely the local manifestations of a systemic disease. They may involve almost any part of the body but particularly the face and fingers. Joint pain is a frequent occurrence. The arthritis often precedes cutaneous lesions, so that the early clinical picture may resemble and may be confused with both rheumatoid arthritis and rheumatic fever. Lymphadenopathy is generally considered to be common. Involvement of the serosal membranes with the formation of effusion is common late in the course of the disease. The signs and symptoms in regard to the cardiovascular system are neither constant nor characteristic of the disease. The total serum protein is usually within normal range, but hyperglobulinemia is reported to be a constant occurrence. Abnormalities of the urine are present in most cases but they are nonspecific. The persistence of the urinary findings with little evidence of progression over long periods suggests that they are a relatively mild reaction to some toxic process.[14] Leukopenia with uniform reduction of all white cells is a feature of this disease. Recently a polymorphonuclear leukocyte containing an inclusion body was described in the peripheral blood and bone marrow of patients with acute disseminated lupus erythematosus. It is hoped that this cell (L.E. cell*) will be of

* The L. E. cell can be found by heparinizing the bone marrow and after waiting for an hour it is located among the polymorphonuclear leukocytes. It may be found in the peripheral blood by centrifugation and observing the L. E. cells in the buffy coat. The L. E. cell can not be differentiated at postmortem study because the hematoxylin bodies in the lymph glands have the same staining qualities. The actual composition of the lupus erythematosus cell is disputed. In our laboratory, we have been unable to find the L. E. cells unless the specimen has been exposed to sunlight. Specimens of blood examined in a darkened laboratory are negative while the same specimens when studied after a period of time in bright sunlight reveal the cells.

great help in the diagnosis of acute disseminated lupus erythematosus in cases exhibiting minimal clinical manifestations.[15–17]

Purpose of the Study

The purpose of this study is to correlate the clinical evidence with pathologic findings in 18 cases of acute and subacute disseminated lupus erythematosus. In review of this disease, special consideration and emphasis has been placed on the clinical and pathologic findings in the cardiovascular system. A careful review of the case studies was made and statistical compilations were recorded in order to correlate specific organ lesions with clinical manifestations due to the collagenous changes as well as noncollagenous lesions.

Table 1.—*The Significant Findings in the Past History of Eighteen Cases of Acute and Subacute Lupus Erythematosus*

Findings	Cases	
	Number	Per cent
Polyarthralgia	13	72.2
Numerous sore throats	5	27.7
Syphilis	2	11.1
Hepatomegaly and splenomegaly of unknown etiology	1	5.5
Sydenham's chorea	1	5.5
Rheumatic fever	1	5.5
Ulcerative colitis	1	5.5
Pernicious anemia	1	5.5
Weakness and numbness of hands and feet	1	5.5

General Observations

Clinical

From 1939 through 1948, 17 cases of acute and subacute disseminated lupus erythematosus were verified by necropsies performed in the Los Angeles County Hospital; with one additional case taken from the files of the Birmingham Veterans Administration Hospital, a total number of 18 cases was studied. A total of 19,242 autopsies were performed. The average autopsy incidence of this condition during this 10 year period was 0.088 per cent. The youngest patient was 17 years of age, and the oldest was 64 years of age. Seventy-seven per cent were in the second and third decades. Seventeen patients were females and only one was a male. Thirteen of 18 cases were Caucasians, 3 were Negroes and 2 were Mexicans.

Joint pains were the most common among the chief complaints of the patients and were encountered in 13 cases. The typical butterfly rash occurred in 11, cough in 6, chest pain in 4, nausea and vomiting in 3, nosebleeds in 1, and vaginal bleeding in 2 patients. Of 13 cases with joint pains, 2 had not had any skin lesions; and of 15 cases with some kind of skin lesion, joint pains preceded skin manifestations by 5, 11, and 12 months, respectively. In each of the 18 cases the pulse rate was above 100 per minute, and each had a high temperature at some time during his illness. Six of 18 cases had ankle edema, but this occurred rather late during the course of the disease. The important findings in the past history of these cases are shown in table 1.

Laboratory

Seventeen of the 18 cases had a hypochromic anemia, in 6 of which the erythrocyte counts were between 2.2 and 3 million per cu. mm.

Fourteen cases had leukopenia. In 4 of these cases the leukocyte count was below 3000; in 5, below 4000; in 2, below 5000 and in 3 cases, below 6000 per cu. mm. In 2 cases, the leukocyte counts were normal and in the other 2 cases slight elevations were noted; 10,000 and 12,000, respectively.

Erythrocyte sedimentation rates were determined in 5 cases. All had a rate between 15 and 41 in the first 60 minutes.

The albumin-globulin ratio was determined in 13 cases. Two of these, had a total serum protein below 5 Gm. In 9 of the 13 cases the globulin determinations of the serum were above 2.5 Gm. and in 2 other cases they were below this amount.

Wassermann and Kahn reactions were negative in all patients.

Cardiovascular System

Clinical Data. Sixteen of 18 cases complained of shortness of breath, but this symptom occurred rather late during the course of disease.

Chest pain was among the chief complaints in 4 of the patients.

Of 17 cases in which blood pressure measurements were recorded 4 showed a diastolic pressure of more than 90 mm. Hg; the highest reading was 240/140.

Three of the 17 cases had a clinically detectable left ventricular enlargement. Apical systolic murmurs were present in 7, a late diastolic rumble in 1, aortic systolic murmur in 1, and an early diastolic murmur in 1 case. Pericardial effusions were diagnosed clinically in 2 cases. Each patient had a regular pulse.

TABLE 2.—*Reported Causes of Death in Eighteen Cases of Acute and Subacute Disseminated Lupus Erythematosus*

Cause of death	Cases	
	Number	Per cent
Bronchopneumonia	5	27.7
Lobar pneumonia	4	22.2
Atypical pneumonia	2	11.1
Bronchopneumonia and uremia	2	11.1
Congestive heart failure and chronic glomerulonephritis	1	5.5
Congestive heart failure and pneumonia	1	5.5
	1	5.5
Toxemia	1	5.5
Hemorrhages	1	5.5
Congestive heart failure	1	5.5

Electrocardiograms were taken in 12 cases. All showed sinus tachycardia. Nine showed some type of abnormality; low voltage was present in 7, T-wave changes in 4, axis deviation in 4, and first degree heart block in 2 cases. Although 9 out of 12 cases had abnormal electrocardiograms no consistent pattern of abnormality was found.

Congestive heart failure with hepatosplenomegaly and edema developed terminally in 3 cases. The shortest duration of the condition from the beginning of the first symptoms to death was five months and the longest six years, with an average duration of two and six-tenths years. As shown in table 2, the cause of death was due to pulmonary complications in 61.1 per cent of the cases.

Pathologic Data. In 14 of the 18 cases studied there was an alteration of the connective tissue and muscle fibers in the myocardium. These changes consisted of fine scars, focal fibrinoid metamorphosis of the collagenous fibers which resulted in fragmentation and swelling of these elements, and increased density of the ground substance. There was a mild perivascular infiltration of the lymphocytes and polymorphonuclear leukotyes, and the myocardial fibers

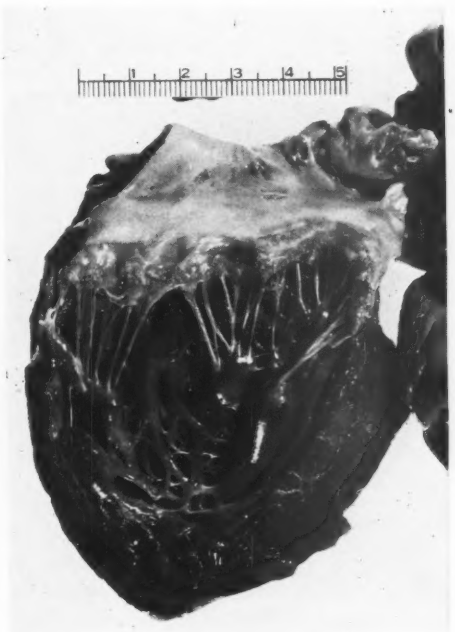


FIG. 1. Case 8, acute nonbacterial verrucous endocarditis (Libman-Sacks type).

were fragmented in some areas. The walls of some small blood vessels showed areas of necrosis of the media, and histiocytic infiltration of the adventitia. The lumen was occluded by hyaline thrombi in some areas. In some cases the only findings were interstitial edema, dense collagen and a few mononuclear cells near the surface. No characteristic Aschoff bodies were seen. Endocardial lesions were present in 8 cases. One of these had subacute bacterial endocarditis of the aortic valve, 1 mitral stenosis and 6 nonbacterial verrucous endocarditis. Figure 1 shows the microscopic findings in the mitral valve of case 8. In this latter case, as seen in the figure, the mitral valve contained many

verrucous vegetations which formed a continuous line across both anterior and posterior leaflets on the auricular surface just away from the free margin of the valve. The posterior cusp of the aortic valve also contained several small verrucous vegetations but the anterior cusp was spared. The commissures were not fused, and the chordae tendineae appeared normal.

Eleven cases had pericarditis. Five of these had pericardial exudates in the respective amounts of 100, 100, 150, 160 and 300 cc. Of

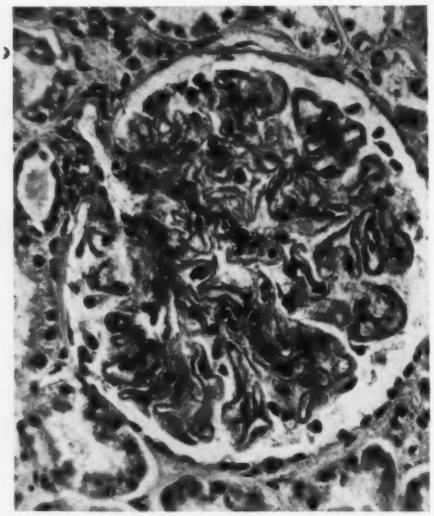


FIG. 2. Case 17, thickening of the basement membrane of the capillary loops (wire-looping).

these 11 cases, 6 had acute pericarditis, and 5 had chronic obliterative pericarditis, 2 of which had pericardiomediastinal adhesions. Three cases had hydropericardium in the amounts of 40 (reddish), 550 and 650 cc.

Two cases had left ventricular hypertrophy. Five cases showed a slight degree of coronary atherosclerosis.

Correlation of Clinical and Pathologic Findings. Of the 18 cases, 16 complained of shortness of breath while 14 cases autopsied revealed definite evidence of pathologic change within the heart. Of 4 cases in which chest pain was one of the most outstanding complaints, necropsy revealed acute pericarditis in 1, pleuritis and pericarditis in 2, and lobar pneumonia in 1 case.

In 4 cases which had hypertension there were found some glomerular changes in the kidneys. These changes will be discussed in the section of kidney pathology.

The pathologic cardiac findings in 7 cases with apical systolic murmurs were as follows: Case 12 had a heart weighing 260 Gm. with no deformity of the mitral valve except two pinpoint-sized nodules on its leaflets. Microscopic examination of these nodules revealed coagulation necrosis with infiltration of lymphocytes, macrophages and a few segmented neutrophiles. Case 2 had obliterative pericarditis with normal valves and no cardiac enlargement. Case 9 had a heart weighing 280 Gm. and the myocardium revealed extreme edema, infiltration with oval and round histiocytes, lymphocytes and eosinophils. The valves were normal. Case 16 showed the changes of subacute bacterial endocarditis on the mitral valve. Case 17 had a heart of 300 Gm. and normal valves. In case 18 the heart weighed 230 Gm. The valves were normal and there was some fibrinoid degeneration in the walls of some vessels in the myocardium.

In case 7, in which a late apical diastolic rumble was heard, autopsy disclosed mitral stenosis. In case 10, which had an aortic systolic murmur, autopsy revealed left ventricular hypertrophy and there were fibrinoid necrotic changes in the endocardium of the aortic and mitral valves present on microscopic examination. As shown by the preceding discussion of 7 cases with apical systolic murmurs, only 2 had nonbacterial verrucous endocarditis of the mitral valve leaflets; conversely, of 6 cases with nonbacterial verrucous endocarditis only 2 had an apical systolic murmur.

In 7 cases in which the electrocardiograms showed some kind of abnormality, the postmortem findings were as follows: Case 1, in which the electrocardiogram showed right axis deviation, low voltage and first degree heart block, autopsy revealed pericarditis with 100 cc. of exudates and small scars in the myocardium. In this case the low voltage can be explained by acute pericarditis, and the heart block by focal small scars in the myocardium. Case 2 had a low voltage, elevated RS-t segments in leads I, II, and III with inverted T

waves in leads III and IV_F. At autopsy, obliterative pericarditis was found. Case 3 had low voltage, and flat T waves in the electrocardiogram. At autopsy acute pericarditis with 100 cc. of exudate in the pericardial cavity was found. Case 4 had low voltage, right axis deviation and first degree heart block. Autopsy revealed obliterative pericarditis and small focal collections of lymphocytes, monocytes and plasma cells in the myocardium. Case 7 had right axis deviation and low voltage of the QRS complexes in the standard extremity leads. Autopsy disclosed 300 cc. of clear, yellow fluid in the pericardial cavity and mitral stenosis. Case 9 had low voltage of the QRS complexes. Necropsy in this case revealed 550 cc. of clear yellow fluid in the pericardial cavity; extreme edema as well as infiltration by oval and round histiocytes, lymphocytes, and eosinophils, were found in the myocardium. Case 11 had left axis deviation, flat T waves in leads I, II and III. At necropsy a chronic pericarditis with petechial hemorrhages, pleuromediastinal adhesions and diffuse petechial hemorrhages in the myocardium were found. Case 15 had low T waves in the standard leads and ventricular premature beats. Autopsy revealed left ventricular hypertrophy, nonbacterial verrucous vegetations on the mitral valve, slight increase in the connective tissue, and numerous small scars in the myocardium. Case 18 had low voltage of the QRS complexes and inverted T waves. At necropsy a pericarditis with 100 cc. of fluid was found.

Urinary System

Clinical Data. Urinalysis was performed in 17 cases. Of these 17, 14 had abnormal findings. All of these 14 cases at some time while under observation showed albuminuria. One showed albuminuria and slight leukocyturia without other clinical evidence or renal disease; one had albumin, leukocytes and granular casts in the urine. Three cases had albuminuria, cylindruria and hematuria; 2 cases had albuminuria, leukocyturia and hematuria; albumin, leukocytes, erythrocytes and casts were found collectively in the urines of 4 cases. Of 17 cases 3 showed no abnormality in the urinalysis at any time while under observation.

Of the 12 cases in which nonprotein nitrogen determinations were done, 7 showed values in excess of the normal of 40 mg. per 100 cc. of blood. In these cases the premortem clinical diagnosis of chronic glomerulonephritis and uremia was made.

Pathologic Data. In each of the 18 cases studied there was some abnormal finding in the kidneys. Thickening of the basement membrane of the capillary loops in the glomeruli with typical "wire-loop" changes was found in 14 cases. Focal necrosis of the loops was present in 2 cases. In 3 cases hyalinization of some glomeruli and scar formations were found. Two cases showed many petechial hemorrhages on the surfaces of the kidneys; one case had numerous pinpoint petechiae throughout the renal cortex; and the other case, hemorrhages into the renal pelvis. One case had chronic glomerulonephritis as well as wire-looping of the glomeruli.

Correlation of Clinical and Pathologic Findings. In each of the 14 cases with abnormal urinary findings necropsy disclosed some abnormality in the kidneys. Cases 3, 5, 8, 10 and 15 had albumin, erythrocytes, leuckocytes and granular casts in their urine, clinically. In each of these cases, except in case 5, wire-loop changes of the glomeruli were found at autopsy. Case 5 had hyalinization of some glomeruli and scar formation. Cases 11, 14 and 16 had normal urinary findings. Autopsy in case 11 revealed moderate thickening of the glomerular capsule, infiltration with round cells, arteriolar thickening and hemorrhages into the pelvis. Wire-loop changes of the glomeruli and hyaline thrombi in the arterioles were noted in case 14. In case 16 wire-looping of the glomeruli and numerous completely hyalinized glomeruli were found. The hemorrhages into the renal pelvis, seen in case 11, might have occurred terminally and have escaped laboratory recognition in this way. In the latter 2 cases urinary findings were normal in spite of the typical wire-loop changes in the glomeruli. One of these 7 cases had numerous necrotic foci and infiltration of leukocytes into the glomeruli, without wire-loop changes. Of 4 cases which developed high diastolic blood pressures over 90 mm. Hg autopsy revealed wire-loop changes

of the glomeruli in cases 3, 15 and 18, and focal-loop necrosis in case 2. In case 15 in addition to marked wire-looping, some glomeruli were shrunken and tubules showed atrophy and replacement by fibrotic tissue in some areas. Why arterial hypertension is not found consistently in the presence of the kidney pathology is not known.

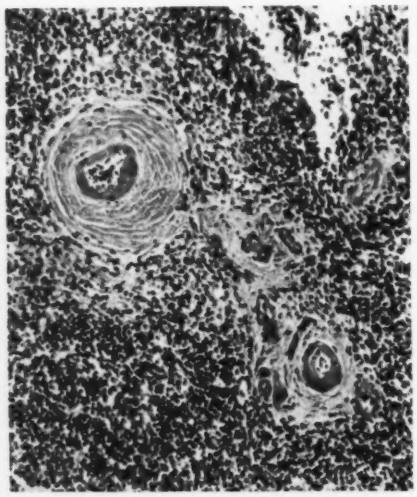


FIG. 3. Case 17, onion peel changes in the central arteries of the spleen.

GASTROINTESTINAL SYSTEM

Clinical Data. Symptoms and signs referable to the gastrointestinal system were not common. One case had hepatomegaly and splenomegaly of unknown etiology for two years. Nausea and vomiting were outstanding complaints in 3 cases. The liver was enlarged to palpation in 6 of the 18 cases and the spleen was enlarged in 6.

Pathologic Data. The pathologic findings in livers of the 18 cases were as follows: 6 cases had slight to moderate degree of fatty degeneration; 1 case had some necrosis of the liver cells; 2 cases had cholelithiasis; 3 cases had some fibrinoid degeneration of the small arterioles and perivascular round cell infiltration; and 6 cases had normal livers.

Alteration of the collagen was found in the spleens of 11 cases. In 10 cases the spleen weighed between 120 and 250 Gm., and in 8 cases between 270 and 480 Gm. Hyperplasia of the malpighian bodies, mild arteritis of the small central arteries with intimal proliferation, the hyperplasia of the adventitia resembling "onion skin," perivascular fibrosis and hemorrhages constituted the significant changes found in microscopic examination of the spleens (fig. 3).

Complete tissue necrosis of the pancreas in one and large areas of pancreatic hemorrhages in another case were found.

Correlation of Clinical and Pathologic Findings. Of 3 cases which complained of nausea and vomiting, case 18 revealed at autopsy moderate fatty degeneration of the liver and typical onion-peel changes in the spleen; case 5 revealed onion-peel changes in the spleen; and case 4, petechial hemorrhages in the mucosa of the stomach. In other cases in which the gastrointestinal tract showed some alteration of the collagen there were no referable clinical symptoms.

RESPIRATORY SYSTEM

Clinical Findings. Dyspnea occurred in 3 cases; chest pain in 5; cough in 6; hemoptysis in 2, and bloody sputum in 1 of the cases. The clinical diagnosis of lobar pneumonia in 5; atypical pneumonia in one; pleurisy in 4; and bronchopneumonia in 3 cases was entertained.

Pathologic Data. Sixteen of the 18 cases had some abnormality in the lungs as follows: 7 cases had bronchopneumonia, 1 of which had also atelectasis; 5 cases had lobar pneumonia; 2 cases had atypical interstitial pneumonia and 1 case had atelectasis. Multiple small hemorrhagic areas scattered throughout the right lung were found in 1 case.

Acute pleuritis was present in 3 cases; chronic pleuritis, in 7 cases. In 5 of the chronic cases both pleural cavities were obliterated by many old, fibrinous adhesions. Three cases had bilateral hydrothorax.

Correlation of Clinical and Pathologic Findings. The correlation of dyspnea, chest pain and cough with pathologic findings showed that these symptoms were due to either (1) inflammation in the lungs, such as pneumonia or bronchopneumonia or (2) pleuritis or (3) some combination of these conditions. Case

11 gave a history of hemoptysis of four week's duration and autopsy findings revealed hemorrhages in the subarachnoid space, in the lungs, pleura, pericardium, myocardium, and into the renal pelvis. Case 13, which had bloody sputum, showed at autopsy some atelectasis in the right lower lobe of the lung. Case 16 had cough, dyspnea and hemoptysis and at autopsy bilateral bronchopneumonia was found.

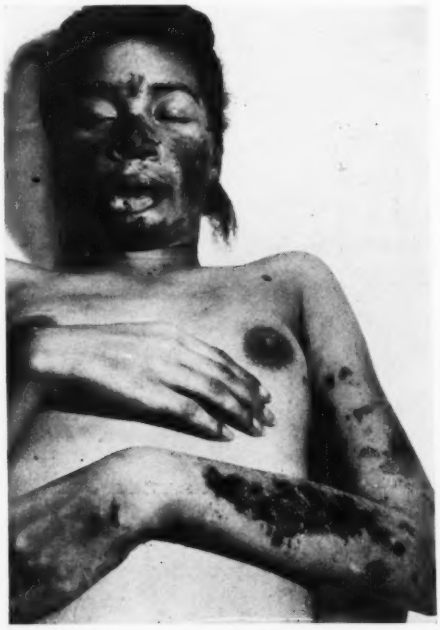


FIG. 4. Case 7, typical rash of butterfly appearanee on the face and erythematous patches on the arm.

SKIN LESIONS

Typical rash of butterfly appearance (fig. 4) occurred in 11 cases. Four other cases had some some other kind of skin lesions, such as dermatitis on the face in 1 case; seborrheic dermatitis in 1 case; and nonspecific erythematous lesions on the trunk in 2 other cases. Of the 15 cases with some kind of skin lesion, joint pains preceded the skin manifestations by 5, 11 and 12 months in 3 such cases.

COMMENT AND SUMMARY

In a study of the clinical and pathologic findings in 18 cases of acute and subacute disseminated lupus erythematosús confirmed at necropsy it has been observed that this disease is more common among females, between the ages of 22 and 33, than males. This is in complete accord with previous observations.

Joint pain was the most common symptom, being encountered in 72.2 per cent of the cases studied.

A rash of butterfly appearance was encountered in 61.1 per cent of the cases. Four other cases had some kind of nonspecific skin lesions. Joint pains preceded skin lesions in only 3 cases, and in others they were either coincident with skin manifestations or occurred some time after them. Two other cases had joint pains for several months but they never had any skin manifestation and autopsy performed in these cases disclosed no lesions of rheumatic fever. This study shows that polyarthralgia due to acute and subacute disseminated lupus erythematosus may occur without any skin manifestation of the disease. In any polyarthralgia with an unknown etiology acute disseminated lupus erythematosus should be considered, although the occurrence of it without skin lesions is not frequent.

The involvement of the heart is very common. In 14 of the 18 cases studied there was an alteration of the connective tissue and muscle fibers in the myocardium. However, there was no constant correlation between clinical findings and specific pathologic lesions found in the heart. Neither murmurs heard over the precordium nor QRS and T-wave changes seen in the electrocardiogram were pathognomonic for the disease. A systolic murmur heard at the mitral area in a patient with disseminated lupus erythematosus might suggest the involvement of the endocardium, but, according to this study, this is usually not the case. Of 7 cases with apical systolic murmurs only 2 had nonbacterial verrucous endocarditis of the mitral valve leaflets; conversely, of 6 cases with nonbacterial verrucous endocarditis only 2 had an apical systolic murmur. Electrocardiographic changes are of clinical significance in that they suggest pericardial or myocardial involvement. Low voltage, elevated RS-T segments, inverted T waves, prolonged P-R interval are indicative of changes in pericardium or in the myocardium, but are not specific for the disease itself.

In the cases studied the most common laboratory finding was albuminuria, this being found in 82.3 per cent of the patients. There was no constant correlation between clinical and specific pathologic findings. The commonly encountered wire-loop changes of the glomeruli may cause albuminuria, leukocyturia, cylindruria, high nonprotein nitrogen of the blood, and hypertension collectively, or one of these signs separately, or there may be no clinical findings.

In the presence of a typical butterfly rash the diagnosis of lupus erythematosus is not difficult, but in 39 per cent of these cases the butterfly rash did not occur. In the absence of the typical skin manifestation, the findings which were most constant and suggestive of the disease were as follows: (1) polyarthralgia of undetermined origin, (2) fever and tachycardia of unknown cause, (3) albuminuria alone, or together with hematuria, and cylindruria, (4) leukopenia, and (5) signs and symptoms of serosal inflammation.

Therefore the diagnosis of disseminated lupus erythematosus should be suspected when a female in the early decades of life presents herself with shortness of breath, a skin rash, multiple joint pains, fever and tachycardia, and in whom there is found evidence of pulmonary, cardiac and kidney abnormality. The diagnosis is confirmed by biopsy of the skin lesion, the finding of an anemia and leukopenia, a high globulin content in the serum (above 2.5 Gm. per 100 cc.) and the detection of typical lupus erythematosus cells in the peripheral blood or in the bone marrow.

REFERENCES

[1] LIBMAN, E., AND SACKS, B.: A hitherto undescribed form of valvular and mural endocarditis. Arch. Int. Med. **33:** 701, 1924.

[2] BAEHR, G., KLEMPERER, P., AND SCHIFRIN, A.: Diffuse disease of peripheral circulation (usually associated with lupus erythematosus and endocarditis). Tr. A. Am. Physicians **50:** 139, 1935.

[3] GUION, C. M., AND ADAMS, E. C.: Six autopsied cases of disseminated lupus erythematosus. Am. J. M. Sc. **205:** 33, 1943.

[4] KLEMPERER, P.: The pathogenesis of lupus erythematosus and allied conditions. Ann. Int. Med. **28:** 1, 1948.

[5] BARBER, H. W.: Effects of sulfonilamide compounds upon lupus erythematosus, especially in cases of streptococcic origin. Brit. J. Dermat. **53:** 1, 1941.

[6] FOX, R. A.: Disseminated lupus erythematosus—allergic disease. Arch. Path. **36:** 311, 1943.

[7] AYVAZYAN, F. AND BADGER, T. L.: Disseminated lupus erythematosus occurring among nurses. New England J. Med. **239:** 565, 1948.

[8] TEILUM, G.: Hyperglobulinemia, periarterial fibrosis of the spleen, and the wire-loop lesions in disseminated lupus erythematosus in relation to allergic pathogenesis. Am. J. Path. **24:** 409, 1948.

[9] BAEHR, G., AND POLLACK, A.: Diffuse vascular disease. Mod. Concepts Cardiovasc. Dis. **15:** 12, 1946.

[10] HUMPHREY, E. M.: The cardiac lesions of acute disseminated lupus erythematosus. Ann. Int. Med. **28:** 12, 1948.

[11] COBURN, A. F., AND MOORE, D. H.: Plasma proteins in disseminated lupus erythematosus. Bull. Johns Hopkins Hosp. **73:** 196, 1943.

[12] KIERLAND, R. R.: Classification and cutaneous manifestations of lupus erythematosus. Proc. Staff Meet., Mayo Clin. **15:** 675, 1940.

[13] MONTGOMERY, H.: Pathology of lupus erythematosus. Proc. Staff Meet., Mayo Clin. **15:** 678, 1940.

[14] KEITH, N. M.: The renal problem in lupus erythematosus. Proc. Staff Meet., Mayo Clin. **15:** 682, 1940.

[15] HARGRAVES, M. M., RICHMOND, H., AND MORTON, R. J.: Presentation of two bone marrow elements, tart cell and L. E. cell. Proc. Staff Meet., Mayo Clin. **23:** 25, 1948.

[16] HASERICK, J. R., AND SUNDBERG, R. D.: Bone marrow as diagnostic aid in acute disseminated lupus erythematosus; report on Hargraves' L. E. cell. J. Invest. Dermat. **11:** 209, 1948.

[17] —, AND BORTZ, D. W.: A new diagnostic test for acute disseminated lupus erythematosus. Cleveland Clin. Quart. **16:** 158, 1949.

[18] GRACE, A. W., AND COMBES, F. C.: Remission of disseminated lupus erythematosus by adenocorticotropin, Proc. Soc. Exper. Biol. & Med. **72:** 563, 1949.

Hepatic Abnormalities in Congestive Heart Failure

Needle Biopsy Studies

By THOMAS J. WHITE, M.D., ROBERT B. WALLACE, M.D., ANGELO M. GNASSI, M.D., NORVAL F. KEMP, M.D., H. PRESTON PRICE, M.D., AND CARROLL M. LEEVY, M.D.

Needle biopsies of the liver were performed on 30 patients with heart failure and correlated with clinical features and biochemical liver function studies. Hepatic biopsy served as a useful adjunct to other methods in deciding the status of the liver in this group. Type of heart disease, degree of heart failure and length of heart failure could not be correlated with the observed histology. Neither history, physical examination, nor biochemical functional studies provided sufficient information to predict anatomy with certainty. A histologic diagnosis improved both therapeutic and prognostic perspective.

THE DEMONSTRATED value of needle biopsy[1] makes an evaluation of its use in studying the liver in congestive heart failure desirable. This is a report of needle biopsies of the liver correlated with clinical features and biochemical studies in 30 patients with heart failure, evaluated after maximum response to a cardiac therapeutic regimen.

MATERIAL AND METHODS

The selected patients were taken from routine ward admissions with congestive heart failure in whom initial appraisal revealed hepatomegaly and/or jaundice. Patients with viral hepatitis, biliary obstruction, malignancy, and hemolytic disease were excluded from these studies. Each patient received cardiotherapy consisting of rest, sodium restriction, diuretics and digitalization. When maximum response to this regimen was obtained as determined by weight changes, venous pressure and circulation time, liver biopsies were performed.

Ages of patients ranged from 30 to 78 years. Eighteen were male and 12 female. Fourteen had rheumatic heart disease; 7 had hypertensive heart disease; 6 had arteriosclerotic heart disease; 2 had constrictive pericarditis; and 1, thyrotoxic heart disease. Congestive failure had been present from 6 months to 10 years. Ten patients had grades II and III functional capacity and 20 had grade IV functional capacity according to American Heart Association standards. Fourteen had auricular fibrillation; 16 had regular sinus rhythm. Hepatomegaly was persistent in 25 patients; in 5 cardiotherapy led to its disappearance. Splenomegaly was present in 11 and jaundice in 6. Ascites refractory to diuretics was present in 14. History revealed alcoholism in 12 patients and poor dietary intake in 15 others.

Biochemical liver function studies consisted in the determination of serum bilirubin,[2] bromsulfalein excretion,[3] total serum cholesterol and cholesterol esters,[4] cephalin cholesterol flocculation,[5] thymol turbidity,[6] serum albumin and globulin,[7] prothrombin time[8] and alkaline phosphatase.[9] Serum bilirubin of more than 1.0 mg. per cent and retention of bromsulfalein of 5.0 per cent or more were considered abnormal. Total cholesterol above or below 150 to 240 mg. per cent with less than 50 to 70 per cent of the total being esterified was classified as abnormal. Three plus to 4 plus cephalin flocculation in 48 hours, thymol turbidity of 5 units or more, serum alkaline phosphatase greater than 5 Bodansky units per 100 cc., and total serum protein of less than 6.8 Gm. per 100 cc. or reversal of the albumin-globulin ratio were considered abnormal.

Liver biopsies were performed with the Vim Silverman needle without complications.[10] Seven patients had serial biopsies. A histologic diagnosis of portal cirrhosis (diffuse fibrosis) was made on the basis of periportal fibrosis, bile duct proliferation, and pseudolobulation with or without hyaline changes, fatty metamorphosis, and lymphocytic infiltration. The diagnosis of hepatic focal infiltration was based on the presence of small intralobular foci of lymphocytes or polymorphonuclear leukocytes not in relation to the central vein, or portal area. Central necrosis was diagnosed by the presence of dead cells or absence of hepatic cells along with condensation of the reticulum around the central vein. Pericentral vein fibrosis was diagnosed by the appearance of condensed reticulum around the central vein. These were interpreted as stages of the classical lesions attributed to congestive failure.[11] The only biopsy specimen showing passive congestion as seen

From the Departments of Medicine and Pathology, Jersey City Medical Center, N. J.

TABLE 1.—*Correlation of Histology and Biochemical Function of the Liver. Clinical Features*

Case No.	Histology	Alcoholism	Dietary Deficiency	Persistent Hepatomegaly	Splenomegaly	Ascites	Serum Bilirubin mg. %	BSP % retention	Serum Cholest. mg. %	Cholest. esters mg. %	Serum Alb. Gm. %	Serum Glob. Gm. %	Ceph. Flocc.	Units Thymol Turb.	Alk. Phos. Units	Prothrombin	Type of Heart Disease	Degree of Heart Failure	Duration of Heart Failure
1	Normal liver	0	0	+	+	0	0	0	—	—	3.6g	*3.9*	*3+*	1U	—	elevated control	HHD	Grade 4	8 yrs.
2	Normal Liver	+	+	0	+	+	*1.2**	0	*109*	*54*	*2.46*	*3.74*	2+	2.0	*5.9*	normal	HHD	" 4	4 mos.
3	Normal Liver	+	+	0	0	+	0.8	*50*	156	93	*1.3*	*4.4*	0	—	—	normal	HHD	" 4	3 mos.
4	Normal Liver	0	0	0	0	0	1.0	—	176	141	—	—	*3+*	0.5	2.5	normal	HHD	" 2	2 yrs.
5	Normal Liver	+	+	+	0	0	0.7	0	154	119	*2.8*	*4.0*	*4+*	5	4.6	elevated	ASHD	" 2	1 week
6	Normal Liver	0	+	+	0	+	0.8	*19.5*	182	119	*2.4*	*3.8*	2+	1	*11.4*	normal	ASHD	" 4	8 mos.
7	Normal Liver	0	+	+	0	0	*1.2*	0	*109*	61	*3.09*	*3.71*	1+	*6.0*	—	normal	ASHD	" 4	2 yrs.
8	Normal Liver	+	0	0	+	0	*5.8*	*33*	165	129	*2.6*	*3.2*	2+	1U	*6.7*	normal	ASHD	" 4	4 mos.
9	Normal Liver	0	0	+	0	+	0.7	0	253	141	*2.24*	1.86	1+	0.5	—	normal	RHD	" 4	6 yrs.
10	Normal Liver	0	0	+	+	0	0.5	*6*	176	109	3.96	2.14	2+	0.5	—	normal	RHD	" 4	10 yrs.
11	Normal Liver	0	0	+	+	0	*2.2*	*16.5*	194	101	*3.3*	*4.2*	0	3.0	—	normal	RHD	" 4	2 yrs.
12	Normal Liver	0	0	0	0	0	0.7	—	159	123	*3.36*	*3.44*	1+	2.0	—	elevated	RHD	" 4	2 yrs.
13	Normal Liver	+	+	0	0	0	*1.2*	*26*	173	—	4.74	2.76	1+	—	—	normal	RHD	" 4	1 yr.
14	Normal Liver	0	0	+	0	+	*1.4*	3	*268*	162	*3.27*	2.53	*3+*	3U	4.6	normal	RHD	" 4	4 yrs.
15	Normal Liver	0	0	+	+	+	—	*7*	*343*	194	*3.27*	2.93	0	3.0	*10.3*	normal	Constrictive Pericarditis	" 4	9 yrs.
16	Normal Liver	+	0	+	0	0	*2.0*	0	*325*	—	3.64	*4.56*	1+	3.5	3.8	normal	RHD	" 4	6 yrs.
17	Normal Liver	0	0	+	+	+	*1.6*	*12.5*	206	103	*3.27*	1.53	neg.	1.5	4.2	normal	Constrictive Pericarditis	" 4	6 mos.
18	Portal Cirrhosis	+	+	+	0	+	—	*9*	—	—	*2.31*	*4.89*	—	—	—	normal	ASHD	" 2	3 yrs.
19	Portal Cirrhosis	+	+	+	0	0	*3.6*	*6*	—	—	*2.7*	*5.4*	0	*8*	*9.4*	normal	HASHD	" 3	1 mo.
20	Portal Cirrhosis	+	+	+	+	+	1.0	*44*	203	*93*	*1.3*	*3.8*	3+	—	—	normal	RHD	" 2	Unknown
21	Portal Cirrhosis	+	+	+	0	+	—	*17.5*	180	*86*	*2.4*	*3.0*	*4+*	3.5	—	normal	RHD	" 2	Unknown
22	Portal Cirrhosis	0	+	+	0	+	*1.4*	1	133	*64*	*3.23*	*3.57*	0	*8.8*	—	normal	RHD	" 4	6 yrs.
23	Portal Cirrhosis	0	+	+	0	+	*2.0*	*45*	213	133	*1.79*	*3.01*	1+	1.0	—	elevated	HHD	" 3	2 yrs.
24	Focal Infiltration	+	+	+	0	0	0.7	—	*299*	171	3.85	2.95	—	0.5	*8.5*	normal	ASHD	" 2	1 yr.
25	Focal Infiltration	+	+	+	+	+	0.1	0.5	*99*	*45*	*3.2*	*4.3*	2+	1.5	—	normal	Thyrotoxic	" 2	1½ yrs.
26	Focal Infiltration	0	0	+	+	0	0.1	*6*	*334*	186	*3.4*	*4.1*	2+	3U	—	normal	RHD	" 4	8 yrs.
27	Focal Infiltration	0	0	+	0	+	1.0	0	151	79	*2.2*	*4.4*	*3+*	—	—	normal	RHD	" 4	3 yrs.
28	Focal Infiltration	0	0	+	+	0	*2.2*	*11.5*	219	126	*3.09*	*3.71*	*4+*	2.0	*7.3*	normal	RHD	" 4	4 yrs.
29	Pericentral Fibrosis	0	+	+	0	0	1.0	—	*133*	*57*	*3.1*	*4.1*	*3+*	—	—	normal	HASHD	" 4	2 yrs.
30	Central Necrosis	0	0	0	0	0	*5.6*	—	165	*49*	*2.61*	*3.89*	*4+*	*7.5*	—	normal	RHD	" 2	6 mos.

* Abnormal values in italics.

in routine autopsy material was the one showing central necrosis. Absence of passive congestion in needle biopsy specimens is due to decrease of blood stasis by needle pressure and tissue tonus, and lack of the agonal dilatation of sinusoidal spaces in postmortem liver sections.[12] Lack of fat in needle biopsy specimens was attributed to the long periods of bed rest prior to the liver studies during which time fat may have been mobilized.[13]

Observations

Seventeen of the 30 needle biopsies showed normal liver histology, 1 with a slight amount of fat. Some of those with normal histology had slight degrees of blood stasis. Six biopsies showed portal cirrhosis. Five biopsies showed focal areas of infiltration with 1 showing a slight amount of fat. One biopsy showed central necrosis with chronic passive congestion and 1 biopsy showed pericentral vein fibrosis.

Of the 17 patients with normal liver on biopsy, 7 had rheumatic heart disease, 4 hypertensive heart disease, 4 arteriosclerotic heart disease and 2 constrictive pericarditis. Of the 6 patients with portal cirrhosis, 3 had rheumatic heart disease, 2 had hypertensive heart disease and 1 had arteriosclerotic heart disease. Of 5 patients with focal infiltration, 3 had rheumatic heart disease, 1 had thyrotoxic heart disease and 1 had arteriosclerotic heart disease. The patient with central necrosis had rheumatic heart disease, and the patient with pericentral vein fibrosis had hypertensive heart disease.

Hepatomegaly disappeared with cardiotherapy in the patient with central necrosis and in 4 of the patients with normal liver histology. Patients with hepatomegaly regressing on cardiotherapy had a greater degree of liver tenderness prior to treatment, and pressure on the liver evoked a more substantial increase in distention of the neck veins.

Correlation of Histology with Clinical Features

Alcoholism and dietary deficiency seemed to be important causes of abnormal histology although such histories were associated with normal liver biopsies in many instances. Four (66.6 per cent) patients with portal cirrhosis, 2 (40 per cent) patients with focal infiltration and 6 (35.3 per cent) patients with normal histology had histories of alcoholism. Prolonged poor dietary intake was present in each of the patients with portal cirrhosis, 2 (40 per cent) patients with focal infiltration, 6 (35.3 per cent) patients with normal histology and the patient with pericentral vein fibrosis.

Neither clinical jaundice, splenomegaly nor ascites could be correlated with biopsy findings. Four of the 6 patients with jaundice had clinical and roentgenologic evidences of lung infarcts. Three of the jaundiced patients had normal liver histology, 2 had portal cirrhosis and 1 had central necrosis associated with congestion. Of 11 patients with splenomegaly, auricular fibrillation was present in 9, with possible embolization to account for splenic enlargement. The spleen was palpably enlarged in only 1 (16.6 per cent) of the patients with portal cirrhosis, whereas 3 (60 per cent) of the patients with focal infiltration and 7 (41.4 per cent) of the patients with normal histology (6 of whom had auricular fibrillation) had splenomegaly. Ascites was present in 7 (41.4 per cent) patients with normal histology, 5 (83.3 per cent) patients with portal cirrhosis, and 2 (40 per cent) patients with focal infiltration. Spider angiomas were present in 2 patients with portal cirrhosis.

The type of heart disease did not determine the type of histology and the degree of heart failure had little influence on the hepatic lesion (table 1). A functional grade of III or IV was given to 12 (70.5 per cent) patients with normal histology, to 3 (50 per cent) patients with portal cirrhosis and to 3 (60 per cent) patients with focal infiltration. Severe failure with grade IV functional capacity was present in the 2 patients with central necrosis and pericentral vein fibrosis.

Heart size, electrocardiographic findings and type of rhythm could not be correlated with liver histology. The duration of heart failure did not apparently determine histopathology. Signs and symptoms of some degree of heart failure had been present continuously for more than one year in 11 (64.7 per cent) patients with normal liver histology and in 3 (50 per cent) patients with portal cirrhosis. Persistent failure was noted for more than eight years in 2 (11.7 per cent) patients with normal liver biopsies and in 1 (16.6 per cent) patient with portal cirrhosis.

Correlation of Histology and Biochemical Functional Studies

Biochemical studies did not provide a clue to the observed histology. Individual patients with normal liver histology had functional patterns closely resembling those of patients with portal cirrhosis, focal infiltration, and pericentral vein necrosis. Serum bilirubin elevation was present in 8 (47 per cent) patients with normal histology, 3 (50 per cent) with portal cirrhosis and 1 (20 per cent) with focal infiltration. Abnormal bromsulfalein retention was present in 8 (47 per cent) patients with normal histology, 5 (83.3 per cent) with portal cirrhosis and 2 (40 per cent) with focal infiltration. Cholesterol disturbances were present in 5 (29.4 per cent) of the normal group, in 3 (50 per cent) of the patients with portal cirrhosis, and in 3 (60 per cent) of those with focal infiltration. Protein disturbances were present in 14 (82.3 per cent) of those with normal liver histology, in all (100 per cent) of the patients with portal cirrhosis, and in 4 (80 per cent) of the group with focal infiltration. Positive cephalin flocculation was present in 4 (23.5 per cent) of the normal group, in 2 (33.3 per cent) of the patients with portal cirrhosis, and in 2 (40 per cent) of those with focal infiltration (table 1).

The following case histories illustrate the difficulties in correlating clinical features, biochemical function and histology:

Case 11. A 47 year old unemployed man with rheumatic heart disease, an enlarged heart, mitral stenosis and insufficiency, auricular fibrillation and with a functional classification of grade IV, had been followed for three and one-half years for recurrent bouts of congestive heart failure. His diet had been adequate and there was no history of alcoholism. He had persistent hepatomegaly and splenomegaly despite disappearance of ankle edema and of pulmonary congestion. Liver function studies revealed intermittent hyperbilirubinemia, increased bromsulfalein retention and abnormal protein patterns. A clinical diagnosis of portal cirrhosis was considered. Two liver biopsies revealed normal histology.

Case 22. A 53 year old housewife with rheumatic heart disease, enlarged heart, aortic stenosis and insufficiency, mitral stenosis and insufficiency, regular sinus rhythm, right bundle branch block and a functional classification of grade IV, had been followed over a period of 14 years for congestive heart failure. There was no history of alcoholism but her diet had been inadequate since the onset of symptoms of congestive heart failure. She was fairly well controlled by digitalis, salt restriction and diuretics. Persistent hepatomegaly without splenomegaly was attributed to chronic passive congestion or "cardiac cirrhosis." Biochemical liver function studies showed elevation of the serum bilirubin with cholesterol and protein changes. Needle biopsy showed portal cirrhosis (fig. 1).

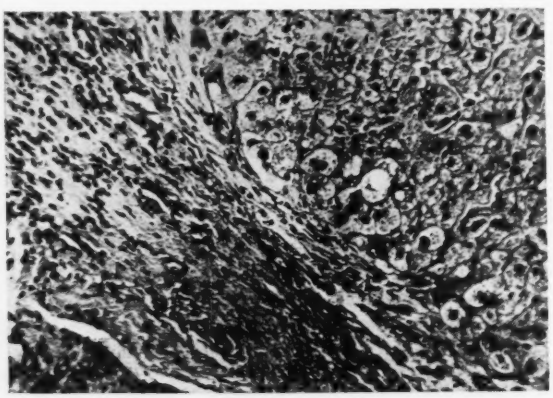


FIG. 1. Case 22. Portal cirrhosis.

Case 24. A 57 year old laborer with arteriosclerotic heart disease associated with angina pectoris, enlarged heart, regular sinus rhythm and grade II functional classification, was admitted with congestive heart failure which had been present for one year. His diet had been good; in early adulthood he had consumed large amounts of whiskey for prolonged periods. Examination showed liver enlargement 8 cm. below the costal margin which persisted after his response to diuretics. Electrocardiograms

showed evidence of an old posterior wall infarction. Biochemical liver function studies were normal except for slight elevations of serum cholesterol and alkaline phosphatase. Needle biopsy revealed small focal collections of lymphocytes as the only abnormality.

Case 29. A 78 year old laborer was admitted for hypertensive heart disease, enlarged heart, auricular fibrillation and grade IV functional classification. Congestive heart failure had been present during the preceding two years. There was no history of alcoholism but his diet had been inadequate for several years. Hepatomegaly, 6 cm. below the costal margin, remained after treatment and it was suspected the patient might have portal cirrhosis. Liver function studies revealed a hypoalbuminemia, total cholesterol and ester ratio disturbance and a 3 plus cephalin flocculation. A needle biopsy showed pericentral vein fibrosis (fig. 2).

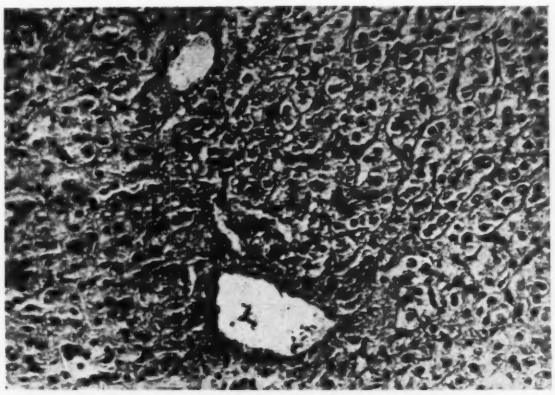


FIG. 2. Case 29. Pericentral vein fibrosis.

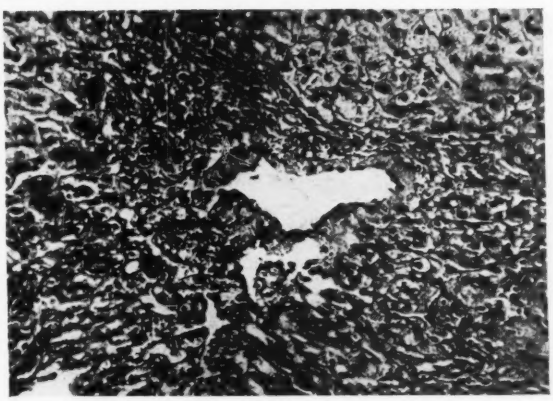


FIG. 3. Case 30. Central necrosis with passive congestion.

Case 30. A 77 year old man was admitted for hemoptysis, fever, and jaundice associated with congestive heart failure. He had rheumatic heart disease, enlarged heart, aortic stenosis and insufficiency, mitral insufficiency and auricular fibrillation. The functional classification was grade IV. His diet had been adequate and there was no history of alcoholism. Chest x-ray films were characteristic of pulmonary infarction. He responded to cardiotherapy and antibiotics with disappearance of hepatomegaly. Biochemical function studies revealed hyperbilirubinemia, hypocholesterolemia, hypoalbuminemia and a 4 plus cephalin flocculation. Needle biopsy showed central necrosis with passive congestion (fig. 3). He improved and was discharged to the cardiac clinic. Nine months later he was readmitted with recurrence of congestive failure, fever and jaundice. He failed to respond to therapy and postmortem examination revealed subacute bacterial endocarditis of the aortic valve. Postmortem liver histology showed central necrosis with passive congestion.

Correlation of Histology with Therapeutic Response

Sixteen (94.1 per cent) of the patients with normal histology, all of the 5 patients with focal infiltration and the 1 patient with pericentral vein fibrosis responded to diuretics with disappearance of ankle edema, ascites and pulmonary congestion although hepatomegaly persisted. Failure to respond to the diuretic regimen in the presence of normal liver histology led to further scrutiny. Renal dysfunction, electrolyte disturbances or infection were then found to be the underlying cause for temporary resistance. On the other hand, despite intensive cardiotherapy the patient with central necrosis and the 6 patients with portal cirrhosis continued to have fluid retention nonresponsive to cardiotherapy. Prognosis in the group with portal cirrhosis was related to the degree of the liver disease; in the others it was determined by the type of heart disease and the severity of congestive failure.

Comment

The limitations of needle biopsy have been fully recognized throughout this investigation.[16] Postmortem examinations of 3 patients in this series corroborated needle biopsy diagnoses. These studies demonstrated a surprisingly high degree of error in the diagnosis of liver changes based on physical and biochemical evaluation. A clinical diagnosis of portal cirrhosis was made in only 3 of the 6 patients proven to have this disorder. Six of 17 patients found to have normal histology and 2 of 5 patients found to have focal infiltration had a diagnosis of portal cirrhosis before biopsy. Diagnostic difficulty arose from attaching undue significance to the type of heart disease, the degree and duration of heart failure, the presence of splenomegaly and the type of biochemical changes seen.

The importance of determining the nature of liver changes in patients with heart failure is illustrated in a review of the cirrhotic group. Continued sodium and protein restriction had been employed in an effort to reduce fluid accumulation. The discovery of a cirrhotic process led to use of a higher carbohydrate and protein food intake. Improvement in diuresis followed although fluid retention persisted. Knowledge of existing cirrhosis also furnished an objective basis for the presenting clinical picture.

Summary and Conclusions

1. Needle biopsies of the liver were performed on 30 patients with congestive heart failure and correlated with clinical features and biochemical function studies. Biopsy revealed normal (histologic) sections in 17 patients, portal cirrhosis in 6, focal infiltration in 5, central necrosis in 1, and pericentral vein fibrosis in 1.

2. Histories of dietary deficiency and alcoholism were related to the observed hepatic changes but were often present with normal histology. Physical examination permitted an accurate diagnosis when correlated with history in some instances, but led the clinician astray in others. Neither jaundice, splenomegaly nor ascites could be correlated with histology. Spider angiomas were seen only in 2 patients with portal cirrhosis. Type of heart disease, degree of heart failure, and duration of heart failure could not be correlated with the observed histology.

3. Biochemical liver function studies did not provide a clue to encountered histology. The dissociation of biochemical tests and histology suggested that the latter was not responsible for the observed liver function changes.

4. Diuretic therapy was more effective in patients with normal histology, focal infiltration and pericentral vein fibrosis. Fluid accumulation was resistant to treatment in patients with cirrhosis and in a patient with central necrosis. Prognosis was related to the degree of liver disease in the patients with portal cirrhosis and to the type of heart disease and severity of congestive failure in the others.

5. Needle biopsy of the liver is a useful adjunct to the history, physical examination and biochemical function studies in determining the state of the liver in congestive heart failure. It permits an anatomic diagnosis and improves prognostic and therapeutic perspective in patients with persistent hepatomegaly associated with heart failure.

References

[16] Iversen, P., and Roholm, K.: On aspiration biopsy of the liver, with remarks on its diagnos-

tic significance. Acta med. Scandinav. **102:** 1, 1939.

[b] SHERLOCK, S.: Aspiration liver biopsy, technique and diagnostic application. Lancet **2:** 397, 1945.

[c] HOFFBAUER, F. W.: Needle biopsy of the liver. J. A. M. A. **134:** 666, 1947.

[d] VOLWILER, W., AND JONES, C. M.: The diagnostic and therapeutic value of liver biopsies. New England J. Med. **237:** 65, 1947.

[e] COGSWELL, R. C., SCHIFF, L., SAFDI, S. A., RICHFIELD, D. F., KUMPE, C. W., AND GALL, C. A.: Needle biopsy of the liver. J. A. M. A. **140:** 385, 1949.

[f] POST, J., AND ROSE, J.: Clinical, functional and histologic studies in Laennec's cirrhosis of the liver. Am. J. Med. **8:** 300, 1950.

[2] MALLOY, H. T., AND EVELYN, K. A.: Determination of bilirubin with photoelectric colorimeter. J. Biol. Chem. **119:** 481, 1937.

[3] MCDONALD, D.: A practical and clinical test for liver reserve. Surg., Gynec., & Obst. **69:** 70, 1939.

[4] BLOOR, W. R., AND KNUDSON, A.: The separate determination of cholesterol and cholesterol esters in small amounts of blood. J. Biol. Chem. **27:** 107, 1916.

[5] HANGER, F. M.: Flocculation of cephalin cholesterol emulsion by pathological sera. Tr. A. Am. Physicians **53:** 148, 1938.

[6] MACLAGAN, N. F.: Thymol turbidity test; new indicator of liver dysfunction. Brit. J. Exper. Path. **25:** 234, 1944.

[7] CAMPBELL, W. R., AND HANNA, M. I.: Albumin globulin and fibrinogen of serum and plasma. J. Biol. Chem. **119:** 15, 1937.

[8] QUICK, A. J.: The Hemorrhagic Diseases. Springfield, Ill. Charles C Thomas 1942.

[9] BODANSKY, A.: Phosphatase studies: determination of serum phosphatase factors influencing accuracy of determination. J. Biol. Chem. **101:** 13, 1933.

[10] WHITE, T. J., LEEVY, C. M., KEMP, N. F., GNASSI, A. M., AND PRICE, H. P.: Needle biopsy of the liver and critical evaluation. J. M. Soc. New Jersey **46:** 549, 1949.

[11a] KATZIN, H. M., WALLER, J. V., AND BLUMGART, H. L.: "Cardiac cirrhosis" of the liver. Arch. Int. Med. **64:** 457, 1939.

[b] BOLAND, E. W., AND WILLIAMS, F. A.: Changes in liver produced by chronic passive congestion with special reference to problem of cardiac cirrhosis. Arch. Int. Med. **62:** 723, 1938.

[c] GARVIN, C. F., AND SCOTT, R. W.: Cardiac cirrhosis. Am. J. M. Sc. **205:** 515, 1943.

[d] FELDER, L., MUND, A., AND PARKER, J. G.: Liver function tests in chronic congestive heart failure. Circulation **2:** 286, 1950.

[12] POPPER, H.: Significance of agonal changes in the human liver. Arch. Path. **46:** 132, 1948.

[13] GILLMAN, T.: Discussion on liver symposium. Gastroenterology **9:** 747, 1947.

Large Thymic Tumor Simulating Pericardial Effusion

By Arthur Bernstein, M.D., Emanuel Klosk, M.D., Franklin Simon, M.D., and Henry A. Brodkin, M.D.

A case of a 20 year old man with a large thymic tumor simulating a pericardial effusion is reported. This tumor, by its position, size and "fluidity," mimicked a pericardial effusion so well that it was only at surgery that a definitive diagnosis could be made. Upon removal of the mass recovery has been complete.

THIS single case of a mediastinal tumor is reported because the tumor surrounded the heart and by its location and shape closely simulated a pericardial effusion. Since mediastinal tumor is not often considered in the differential diagnosis of what is apparently an enlargement of the cardiac silhouette itself, this case should serve as a stimulus to more inclusive diagnostic thinking.

Case Report

A 20 year old Negro male, a grocery clerk, was first seen on Aug. 29, 1949. About six weeks before this, the patient had had a routine chest x-ray film made when he applied for a food handler's certificate of health. He was told that he had fluid around his heart and would require hospitalization. He was then sent to the Newark City Hospital where he was observed for 27 days. While hospitalized, attempts to aspirate "fluid" were unsuccessful, and surgery to remove the "fluid" was proposed. The patient, however, refused and left the hospital to go under the care of his private physician.

The patient had been entirely asymptomatic. His appetite was good and there had been a weight gain of 7 pounds in the past year. There had been no chest pain, no cough, no dyspnea, no fever, no night sweats, no expectoration or hemoptysis and no weakness nor loss of strength. He worked daily as a grocery clerk and delivery boy.

The family history was not remarkable. The patient had lived in Florida until 1946 and was in good health except for a "mild" attack of pneumonia at the age of 10 years. The history suggested asthma at 15 years of age.

Physical Examination. The patient was a thin Negro man, 5 feet 8 inches tall, weighing 119 pounds, without dyspnea, orthopnea, or cyanosis. Examination of the eyes, ears, nose and throat showed no significant abnormality. The neck veins were not distended. There was no thyroid enlargement nor lymphadenopathy. The precordium showed no bulge. There was bilateral gynecomastia. The area of cardiac dullness was increased to the right and left on percussion. Heart sounds were distant and varied when the patient was changed from the upright to the recumbent position, being somewhat louder in the recumbent than in the upright position. The rhythm was regular with a pulse and ventricular rate of 80 per minute. The blood pressure was 110/70 in both arms. There were no significant changes in auscultation or percussion of the lungs. Abdominal examination revealed no masses or palpable viscera. There was no ascites or pitting pretibial edema. Rectal examination, including a sigmoidoscopic investigation, failed to reveal any pathologic changes. Neurologic examination was within normal limits. The genitalia were those of an apparently normal adult male.

X-ray of the chest showed a roughly triangular density obscuring the normal cardiac shadow. The apex of the triangle was at the manubrium of the sternum, and the sides sloped downward and laterally to reach the left lateral chest wall at the level of the eighth rib on the left and almost to reach the lateral chest wall on the right. On the lateral view, the density had a posterior border which sloped downward and posteriorly reaching to the posterior chest wall. Anteriorly the mass extended upward along the anterior chest wall reaching almost as high as the manubrium. No pulmonary infiltration was seen. On a film taken in full expiration, there was definite upward displacement of the triangular shadow with increased convexity of its lateral borders. Fluoroscopy revealed that the major portion of this density was in the anterior portion of the chest and sloped gradually toward the level of each hemidiaphragm, encroaching on the posterior inferior portions of the thorax. In the upright position, faint but definite systolic expansile pulsations were noted in the upper halves of this density, along both its right and left margins, becoming less prominent as the bases were approached. These expansile pulsations were extremely minimized when

From The Newark Clinical Group and Newark Beth Israel Hospital, Newark, N. J.

the patient was put in a supine position. The assumption of a supine position resulted in a broadening of the superior portion of this silhouette and replacement of the straightened lateral margins by a

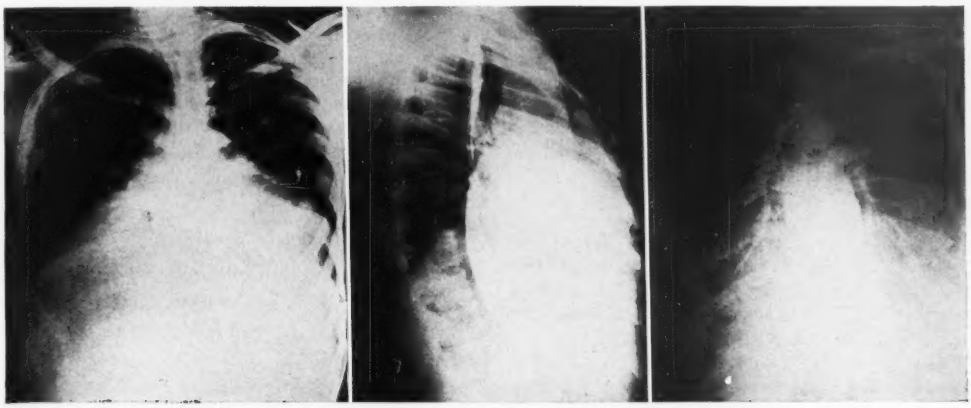


FIG. 1. X-ray films before operation. These demonstrate the size and shape of the mass, as well as the normal size of the heart within the tumor as shown by the angiocardiogram.

convexity. There was posterior displacement of the barium filled esophagus both in the right and left oblique positions (fig. 1).

The electrocardiogram was essentially normal except for flat to diphasic T waves in precordial leads $CF_{3, 4, 5, 6}$ and the electrical pattern did not change with positional change of the patient. A Master two step tolerance test was interpreted as normal (fig. 2).

The venous pressure was 140 mm. with no change on liver pressure. The circulation time was 10 seconds with saccharine and 8 seconds with ether. Patch test and Mantoux (1:1000) were negative. Laboratory studies showed a normal hemogram with 4,100,000 red blood cells, 13.4 Gm. of hemoglobin, 9,200 white blood cells with a normal differential count. The urea nitrogen was 10.9 mg. per 100 cc. and the blood sugar 104 mg. per 100 cc. The total protein was 7.05 Gm. per 100 cc. with an albumin of 4.00 Gm. and globulin of 3.05 Gm. and an albumin-globulin ratio of 1.3:1. The cephalin-cholesterol flocculation test after 48 hours was read as 1 plus and the thymol turbidity as 3.7 units. The sedimentation rate was 17 mm. in 60 minutes and the Kahn test was negative. Routine urinalyses were normal. A two-hour rat pregnancy test was normal.

Though the presumptive diagnosis was that of pericardial effusion we were most impressed with the absence of other clinical findings that are so commonly found in this condition. Chest tomography and angiocardiography were helpful only in establishing the fact that there was a normal size heart surrounded by a mass of a type which could not be determined. Gastrointestinal series and barium enema failed to reveal any evidences of herniation of subdiaphragmatic structures into the chest. An intravenous urogram failed to reveal any evidences

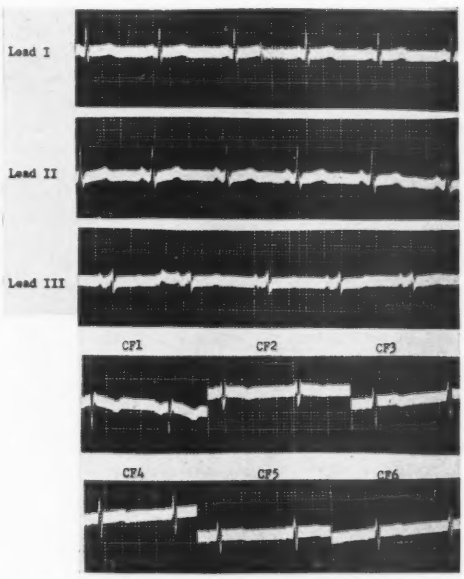


FIG. 2. Electrocardiogram taken when the patient was first seen. The flat to diphasic T waves in the precordial leads are readily apparent.

of any renal tumor or any suggestion of a perirenal mass.

Pericardial aspiration was then attempted in the third, fourth, fifth and sixth intercostal spaces to the right and left of the xiphochondral junction using a

16 gage needle. No fluid or tissue was obtained. Having considered the possibility of this being one of the lymphomatous conditions, a lima bean shaped node was removed from the left subinguinal region which microscopically showed only a reactive lymph node with fibrosis.

The patient was then followed for the next five months without any change in his general condition. In view of the fact that there was a definite uncertainty as to the diagnosis in this case, it was decided that it would be justified to do an exploratory thoracotomy in the hope of establishing a diagnosis. On Feb. 13, 1950 a left thoracotomy was done at The Newark Beth Israel Hospital by Dr. H. Brodkin. A large tumor mass was found which wrapped around the heart much like a vest buttoned in the back. Because of its size it was removed in two stages, the second stage being done 11 days after the first. The patient's recovery was essentially uneventful. The specimen in its entirety weighed 2810 Gm. Grossly it appeared to be a lobulated mass of yellow-gray tissue which was irregular in shape. The first portion removed measured 20 cm. in length, 20 cm. in width and was 8 cm. thick, and the second portion was 55 cm. long, 14 cm. wide and 5 cm. thick. The lobulated tissue showed focal hemorrhagic discoloration of its surface. Section through the tissue revealed linear irregular areas of gray tissue having a granular appearance, the granularity being due to yellow flecks in the gray background. These irregular areas of gray tissue were surrounded by an abundance of yellow tissue resembling fat. This appearance was present with uniform consistency throughout the entire tumor (fig. 3).

Microscopic section of the left side of the tumor showed well differentiated thymoma with pleomorphic epithelial proliferation (fig. 4). The right side of the tumor also showed well differentiated thymoma but appeared to be relatively greatly reduced in comparison to the left portion. Furthermore, the epithelial component in this part of the tumor was much more prominent, but the pseudoglands seen in the previous specimen were not found.

When seen the day after he left the hospital, the patient was found to have a fluid collection in right paracardiac area of the mediastinum, the site of the dead space left after removal of the tumor. From our findings at the first operation, at which time we removed large blood clots from the left pleural space, this was believed to be clotted blood. The patient was observed another week following which aspiration was attempted and 50 cc. of dark brown thick fluid containing blood clots was removed with difficulty. Four days later 200,000 units of streptokinase was instilled after another 150 cc. of the same dark brown fluid had been removed. Two days later over 500 cc. of dark brown fluid was easily removed, the fluid having thinned out remarkably. Three days later another 400 cc. of fluid was removed, and repeated x-ray films revealed a clearing of the "fluid" shadow.

The patient's recovery has been excellent and at the present time he offers no complaints whatsoever. He is working at his usual job with his usual good tolerance to effort.

When last examined on Aug. 18, 1950, his condition had returned to normal but the most interesting finding was the fact that his electrocardiogram now had normally upright T waves in the precordial leads instead of the flat to diphasic T waves which had been present originally (fig. 5).

Discussion

It is apparent from the description, x-ray films and electrocardiographic findings that this tumor caused confusion in diagnosis because of the fact that it more or less enveloped the heart and showed none of the usual eccentric enlargements seen with mediastinal tumors. Furthermore, its high fatty content and the "fluidity" of this tissue served to further confuse the issue because it acted much like a pericardial effusion would when the patient assumed the upright and recumbent positions. However, several findings mitigated against the diagnosis of pericardial disease of a massive type. In the first place there was an absence of significant cardiac findings since the patient was able to do hard work. Furthermore, there was an absence of the usual signs such as small pulse pressure and changes in the electrocardiogram. Again, repeated aspirations failed to yield any fluid. The possibility of lobulation or thick adhesions, as occasionally observed in tuberculous pericardial disease, was considered, but since the patient worked and felt so well we did not believe that this was probable. It was difficult to conceive that any of the usual types of pericarditis could produce this picture without reducing the patient to a state of invalidism.

In reviewing the literature we find only 2 cases reported that are similar to the one herein described. Andrus and Foote[1] removed a 2235 Gm. tumor containing fat and thymic tissue from a 13 year old boy and Hall[2] found an 1100 Gm. thymus- and fat-containing tumor in a 47 year old laborer killed accidentally. In both these cases, it should be noted that the tumor was actually in one of the pleural cavities pushing the heart aside rather than enveloping it.

McCorkle and co-workers[3] have described 34 cases of benign lipomas which simulate the tumor found in this case in their general contour and mobility but differ histologically. They describe one lipoma which weighed 16 pounds when removed at autopsy. In addition, the literature records much discussion on the use of the term thymoma to describe mediastinal tumor as well as the structures upon which it pressed or which it distorted. The amount of fat, and therefore, the mobility and fluidity of the tumor are also important in that they govern the ability of the tumor to adjust to the surrounding structures rather than to obstruct and displace them.

In our case, the gynecomastia was also of some interest to us. Because of its presence we suspected the possibility of a teratoma of the testicle with metastasis and, accordingly, did the two hour rat test for gonadotropins in the urine. As noted, this was negative. In searching for another explanation for this phenomenon, we found the discussion of gynecomastia by Fried very illuminating. He showed that, in the presence of tumors of the lung, gynecomastia was found in many cases.[10] He believed that this, along with other of his findings,

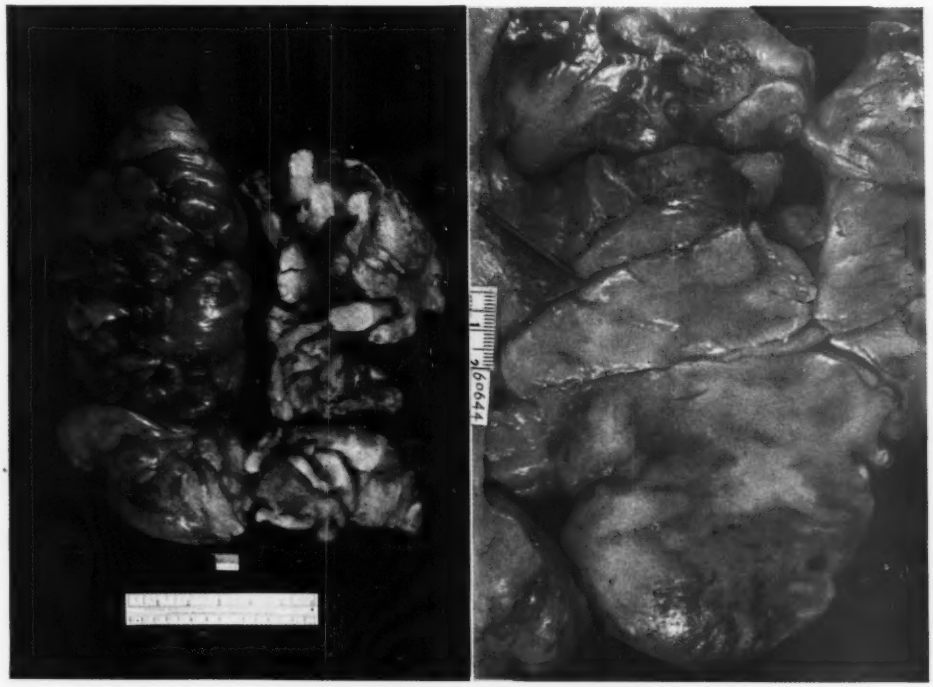


FIG. 3. The two halves of the mass, as well as the appearance of the cut surface are shown. The linear irregular areas of gray tissue having a granular appearance are also apparent. The preservation made necessary by removal of the left half of the tumor 11 days before the right resulted in shrinkage and loss of color. (*The use of color in this illustration has been made possible by a grant from Wyeth Incorporated to the publication fund of the American Heart Association.*)

tumors containing fat and thymic tissue.[4–9] However, under the circumstances, this matter is not pertinent to this discussion and will be left to a further report based on the microscopic pathology. The relation of thymic tumors to myasthenia gravis also need not be discussed here since the patient had no symptoms of this disease.[7–9]

The symptomatology in the reported cases varied from none to dyspnea, cough and cyanosis depending upon the size and location of the

proved that the lung is an organ of internal secretion in addition to its other functions. breast enlargement has disappeared since the removal of his tumor.

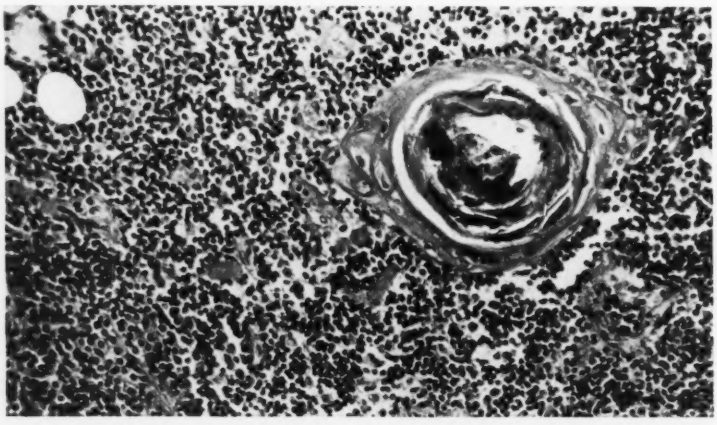


FIG. 4. Section of the thymic tumor showing well developed Hassall's corpuscle, lymphoid and reticular cells and fat cells. H & E, 180×.

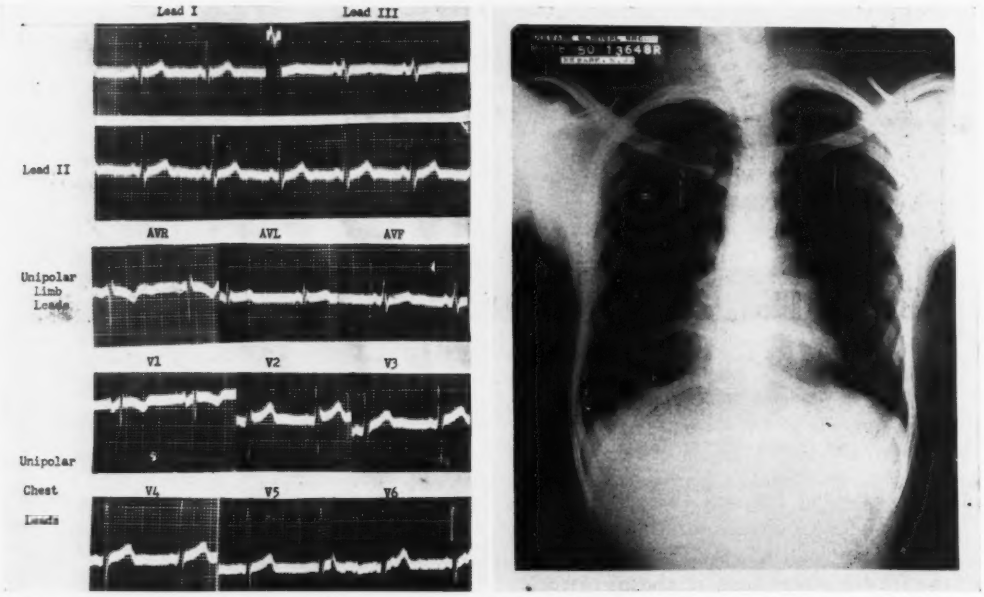


FIG. 5. X-ray film and electrocardiogram taken at the time of the patient's last visit. The lung fields have now entirely cleared. The electrocardiogram shows upright T waves in the precordial leads, as well as an increased voltage of the QRS complexes.

Though our patient did not have a tumor of the lung, there was some lung compression by this mass and it is most interesting that the

Another point worthy of note was the use of streptokinase[11] to dissolve the postoperative blood clot so that it could be aspirated and so

speed the recovery of the patient. It is possible that if permitted to remain, this mediastinal collection of blood may have been a source of trouble to the patient in later years if not immediately.

The findings in this case justify the statement that a thymic tumor containing a large amount of fat may simulate a pericardial effusion because of its ability to accommodate itself to the structures surrounding it and be shaped by them rather than distort them. Therefore, though a rare occurrence, it must be considered in the differential diagnosis of pericardial effusion.

Summary

1. An asymptomatic thymoma weighing 2810 Gm. which was discovered by a routine chest roentgenogram is reported.

2. Because of its "fluidity" it adjusted itself to surrounding structures and simulated pericardial effusion.

3. The necessity of adding thymic tumor to the conditions which must be differentiated from pericardial effusion and the relationship of mediastinal tumor to some cases of gynecomastia is demonstrated.

4. The value of streptokinase in liquefying postoperative mediastinal hematomas was again demonstrated.

Acknowledgments

The authors wish to thank Dr. Thomas M. McMillan and Dr. Samuel Bellet for their suggestions and advice with this case. We also wish to thank Dr. Milton Kannerstein, Pathologist of The Newark Beth Israel Hospital, for his study of the mass and its sections. We are indebted to Doctors S. Sherry and W. S. Tillett for making the streptokinase available to us for use in this patient.

References

[1] Andrus, W. De W., and Foote, N. C.: Report of a large thymic tumor successfully removed by operation. J. Thoracic Surg. **6:** 648, 1936–1937.

[2] Hall, G. F. M.: A case of thymolipoma. Brit. J. Surg. **36:** 321, 1949.

[3] McCorkle, R. G., Koerth, C. J., and Donaldson, J. M.: Thoracic lipomas. J. Thoracic Surg. **9:** 568, 1939–1940.

[4] Margolis, H. M.: Tumors of the thymus; pathology, classification and report of cases. Am. J. Cancer **15:** 2106, 1931.

[5] Crosby, E. H.: Malignant tumors of the thymus gland. Am. J. Cancer **16:** 461, 1932.

[6] Symmers, D.: Malignant tumors and tumor-like growths of the thymic region. Ann. Surg. **95:** 544, 1932.

[7] Norris, E. H.: The thymoma and thymic hyperplasia in myesthenia gravis with observations on the general pathology. Am. J. Cancer **27:** 421, 1936.

[8] —: A thymoma (adenoma of the thymus) from an unusual case of myasthenia gravis, with observations on the general pathology. Am. J. Cancer **30:** 308, 1937.

[9] Murray, N. A., and McDonald, J. R.: Tumors of the thymus in myasthenia gravis. Am. J. Clin. Path. **15:** 87, 1945.

[10] Fried, B. M.: Bronchiogenic Carcinoma and Adenoma. Baltimore, The Williams & Wilkins Co., 1948. Pp. 213–220.

[11] Sherry, S., Tillett, W. S., and Read, C. T.: The use of streptokinase-streptodornase in the treatment of hemothorax. J. Thoracic Surg. **20:** 393, 1950.

Anatomic Variations of the Orifice of the Human Coronary Sinus

By HERMAN K. HELLERSTEIN, M.D., AND J. LOWELL ORBISON, M.D.

Anatomic variations of the orifice of the human coronary sinus now have practical significance since the advent of catheterization of the coronary sinus. Six main types of variation of the valve of the coronary sinus of 150 hearts are described. The difficulties encountered in catheterization of the human coronary sinus are probably due to obstruction offered by large membranes, bars and networks, and less frequently due to the presence of a large eustachian ridge. On the basis of this study, catheterization of the human coronary sinus should be possible in a maximum of 75 per cent of the cases.

MEASUREMENT of the coronary blood flow and myocardial metabolism[1-5, 7] has been made possible by the technic of catheterization of the coronary sinus in the intact dog and man. Detailed knowledge of the structure of the right atrium, and particularly of the variations and anomalies of the venous valves of the right atrium of the human heart (eustachian valve or the valve of the inferior vena cava, and the thebesian valve or the valve of the coronary sinus) now has practical significance. The failures reported in a large per cent of the attempts to catheterize the human coronary sinus can be explained on anatomic bases. Since in previous studies[8-10] the anatomic variations of the human coronary sinus were not considered from the viewpoint of their possible influence on catheterization, we believe it desirable to study anew the variations in the orifice of the human coronary sinus in a large series of adult hearts.

MATERIALS AND METHODS

We have studied the eustachian and thebesian valves and the orifice of the coronary sinus in 150 hearts chosen at random from the large collection of formalin fixed specimens at the Institute of Pathology, Western Reserve University. The hearts had been opened in the customary routine manner, so that the eustachian valve was usually sectioned near the middle by an incision extending between the orifices of the venae cavae. In examining the eustachian valve, special care was taken to reappose the cut edges, and examine its structure from the lateral aspect of the opened right atrium. The thebesian valve and orifice of the coronary sinus were intact in each case.

All descriptions and measurements of the valves were made with the heart held in a position similar to that occupied in the intact body—the superior and inferior venae cavae in an axis parallel to the longitudinal axis of the body, with the longitudinal axis of the heart (base to apex) semihorizontal. Observations made in recent autopsies confirmed the correctness of the above position (fig. 1). When the free wall of the right ventricle and the anterior lateral aspect of the right atrium are removed from a heart in situ, the following relations are observed: the free margin of the eustachian valve is concave and is directed cephalad, and the attached margins extend roughly from dorsum to ventrum, parallel to the median sagittal plane of the body. The orifice of the coronary sinus is to the left and below the medial extremity of the valve of the inferior vena cava and in the space between the latter and the edge of the right atrioventricular orifice. The form and the position of the thebesian valve will be described in detail later. The right atrioventricular ring forms an acute angle with the long axis of the body. Hence, the longitudinal axis of the heart (center of the base to the apex) forms an obtuse angle with the long axis of the body. These details are presented because in previous reports[9] descriptions and measurement were given for a heart held with the long axis *vertical*.

The following measurements were made: maximum and minimum diameters of the coronary orifice; maximum height of the thebesian valve (from attached to free edge); and width of the eustachian

From the Department of Medicine, University Hospitals of Cleveland, Ohio, and the Institute of Pathology, Western Reserve University School of Medicine, Cleveland, Ohio.

This work was done while one of the authors (H. K. H.), was Post Doctorate Research Fellow of the National Institutes of Health of United States Public Health Service, 1949.

This project was aided by a grant from the Youngstown Area Heart Association.

Presented at the First International Cardiological Congress, Paris, France, September 4, 1950.

ridge in the vicinity of the orifice of the coronary sinus. These measurements have relative value only, since the hearts had been preserved in formalin, which produces significant shrinkage. In the living patients, the values undoubtedly are greater. Other observations included heart weight and objective evidence of congestive failure: dilatation of the heart, flattening of the columnae carnae, ascites, pleural effusion and passive hyperemia of liver, lungs and spleen.

The maximum diameter of the orifice of the coronary sinus was obtained by inserting gently a tapered glass tube and measuring the diameter with a vernier caliper to the nearest millimeter. The minimum diameter was that of the orifice not covered by the thebesian valve. Thus if the thebesian valve was a large simple fold, and covered the entire orifice, the minimum diameter was considered to be zero, while the maximum diameter was perhaps 6 mm., since it admitted such a probe when the free edge of the valve was lifted anteriorly (ventrad).

As each specimen was examined, the ease of catheterization was estimated, taking into account the obstruction offered by the eustachian ridge and the thebesian valve, and the diameters (maximum and minimum) of the orifice of the coronary sinus.

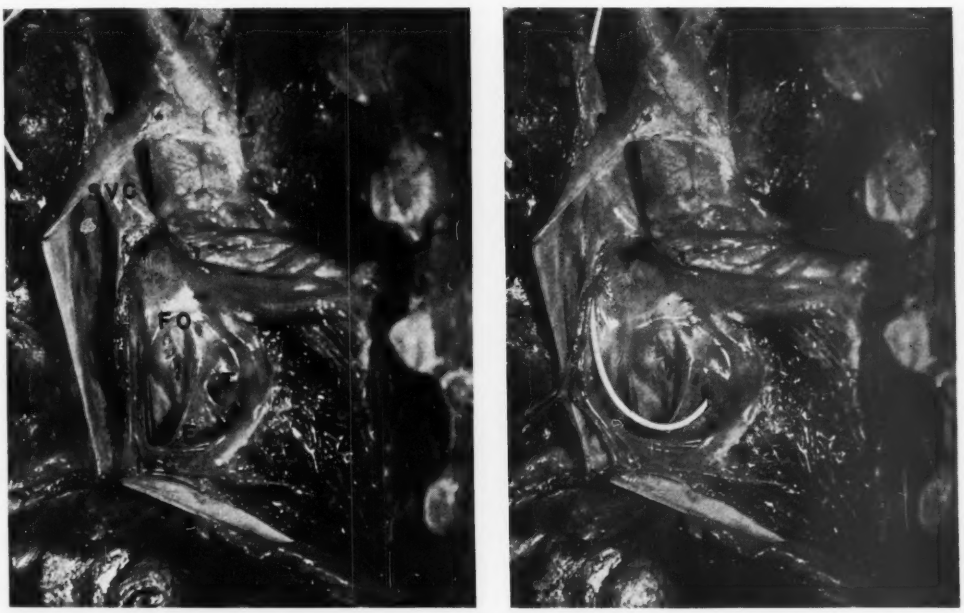


FIG. 1. Heart in situ. The anterior wall of the chest, right atrium and right ventricle were removed without disturbing the position of the heart. Note that the orifice of the coronary sinus, partly covered by a semilunar membrane (*T*, thebesian valve), is situated to the left and below the medial extremity of the eustachian valve, *E*. On the right, the catheter tip has entered the orifice of the coronary sinus and is directed dorsad. *F.O.*, fossa ovalis; *SVC* and *IVC*, superior and inferior vena cava, respectively.

OBSERVATIONS

A comparison of the age, sex and color distribution of the subjects from whom this series of 150 hearts were obtained with a previous study of 2000 consecutive autopsies[14] indicated that the hearts studied are representative of the adult autopsy population encountered at the Institute of Pathology. Seventy-seven per cent were white, and 23 per cent Negro; 61 per cent males, 39 per cent females; the ages ranged from 24 to 84 years, with 67 per cent of the cases between 50 and 79 years of age. The incidence of congestive heart failure was also similar—24 per cent. The slight difference between the previous and present series is due to the exclusion of children in the latter.

Location of the Orifice of the Coronary Sinus. The orifice of the coronary sinus with its valve lies directly below the medial extremity of the eustachian valve, and in the space between

the latter and the rim of the right atrioventricular ring. This saccular space or depression has been called the appendix auricularis posterior of His, or the subeustachian sinus of Keith.[9] In 1 case, however, there were two orifices of the coronary sinus: one was diminutive and was located in the usual position; the second orifice was larger and opened into the left atrium in the middle of the posterior wall just above the mitral valvular ring (fig. 2). There was no evidence that the latter was an acquired anomaly. Since this series was completed, a similar variation was observed in the heart of a patient in whom a Beck aorta–coronary sinus anastomosis[12] was made because of severe obliterative coronary arteriosclerosis. In this particular case, this anomaly had clinical significance, since its patency constituted an aortic–left atrial communication, and precluded the maximum benefit of the operation.

TABLE 1.—*Variations of the Thebesian Valve (150 Cases)*

	Number Cases	Per Cent Total
Absent	22	14.7
Thebesian valve absent	12	
Both thebesian and eustachian valves absent	10	
Small Crescentic Membrane	57	38.0
Simple nonfenestrated	47	
Simple nonfenestrated with strands, threads	5	
Simple fenestrated	3	
Double crescentic	2	
Large Membrane	46	30.7
Nonfenestrated	34	
Nonfenestrated with strands	1	
Fenestrated	10	
Circumferential fenestrations only	1	
Bars, Broad Fibrous Bands, with Strands	8	5.3
Transverse bar	5	
Vertical bar	2	
Oblique bar	1	
Threads, Strands, Networks	8	5.3
Strands	7	
Network	1	
Common Eustachian and Thebesian Valves	9	6.0
Thebesian crescentic	3	
Thebesian semilunar, nonfenestrated	2	
Thebesian semilunar, fenestrated	1	
Thebesian network (with Chiari, 2)	3	
		100.0

Variations of the Thebesian Valve. The structure of the thebesian valve varies anatomically more than that of the eustachian valve,[8, 9] but may be readily classified into six anatomic groups (table 1). Our classification is modified from that used by Wright, Anson and Cleveland,[8] and lends itself more readily in evaluating the feasibility of catheterization than the more detailed classification of Yater.[9] In later observations on the hearts of several hundred routine autopsies, the thebesian valves were of similar types.

(1) The thebesian valve was absent in 14.7 per cent (22 cases) (fig. 3). The coronary sinus communicated directly with the right atrial cavity. In 10 of the 22 cases, the eustachian valve was also absent.

(2) In 38 per cent (57 cases), the thebesian valve consisted of a narrow rim, ridge or membrane, attached to the right and inferior region of the orifice of the coronary sinus (fig. 4). The valve was crescentic, and its free edge was concave, anterior, and directed cephalad. The height of the valve (from free to attached edge) averaged 2.6 mm., with a range of 1 to 5 mm. In each instance the valve covered less than half of the orifice of the coronary sinus, and certainly could not have prevented the regurgitation of blood from the atrium into the coronary sinus. By the same token, in these cases, catheterization of the coronary sinus would be feasible. In 3 cases of this group, there were fenestrations, usually multiple, varying in shape from circular to oval, and with diameter from 0.5 to 2 mm. In 5 cases there were single or multiple fine strands or threads in addition to the crescentic fold. These threads ran horizontally, and were attached to the superior (cephalad) region of the coronary orifice. In 2 cases there was a double crescentic fold in the right inferior region of the coronary

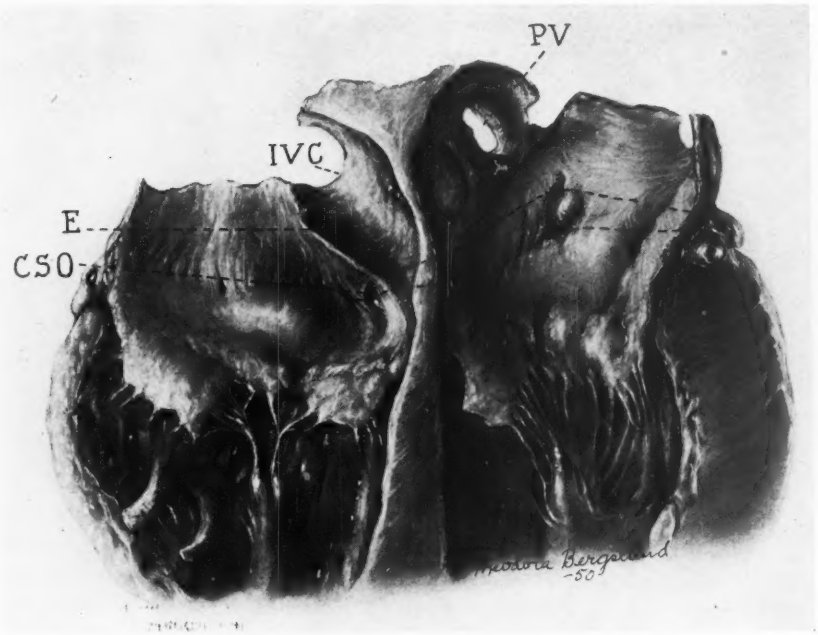


FIG. 2. A-10158. Unusual heart with two orifices of the coronary venous system; one in the right atrium (*RA*) and the other in the posterior wall of the left atrium (*LA*) just above the mitral ring. Note that the eustachian ridge is absent.

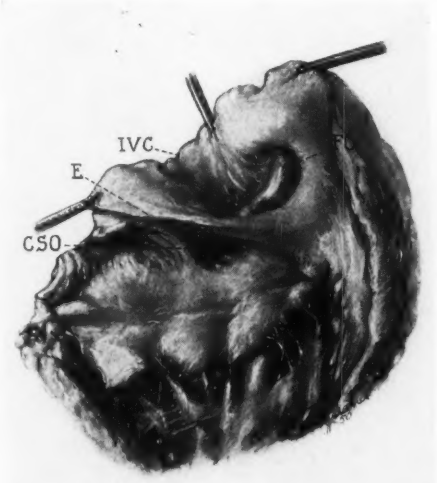


FIG. 3. A—10036. Thebesian valve is completely absent. The diameter of the orifice of the coronary sinus measured 9 mm.

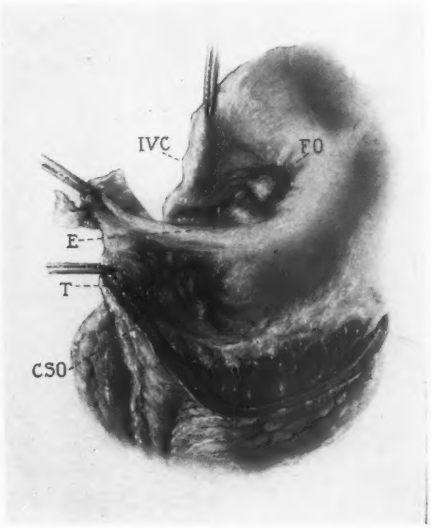


FIG. 4. A—11018. Thebesian valve is a narrow crescent, measuring 2 mm. in maximum depth.

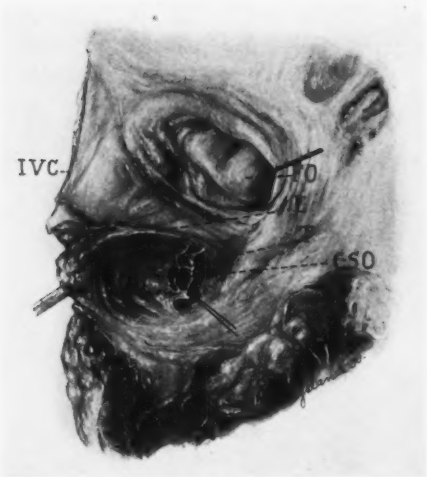


FIG. 5. A—11019. Thebesian valve is a large membrane (9 mm. in depth) with large fenestrations at the free margin. The maximum diameter of the coronary orifice was 7 mm.

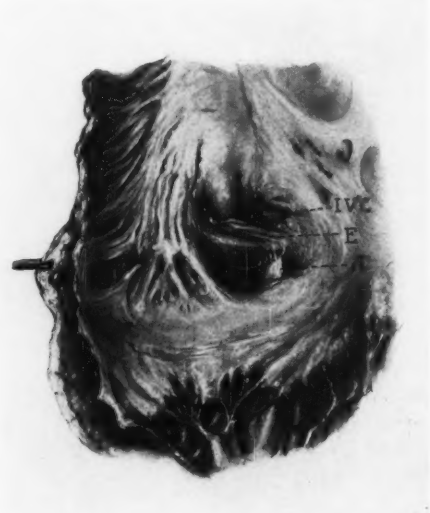


FIG. 6. A—9800. Thebesian valve is a large membrane with circumferential perforations, and covers the orifice of the coronary sinus completely.

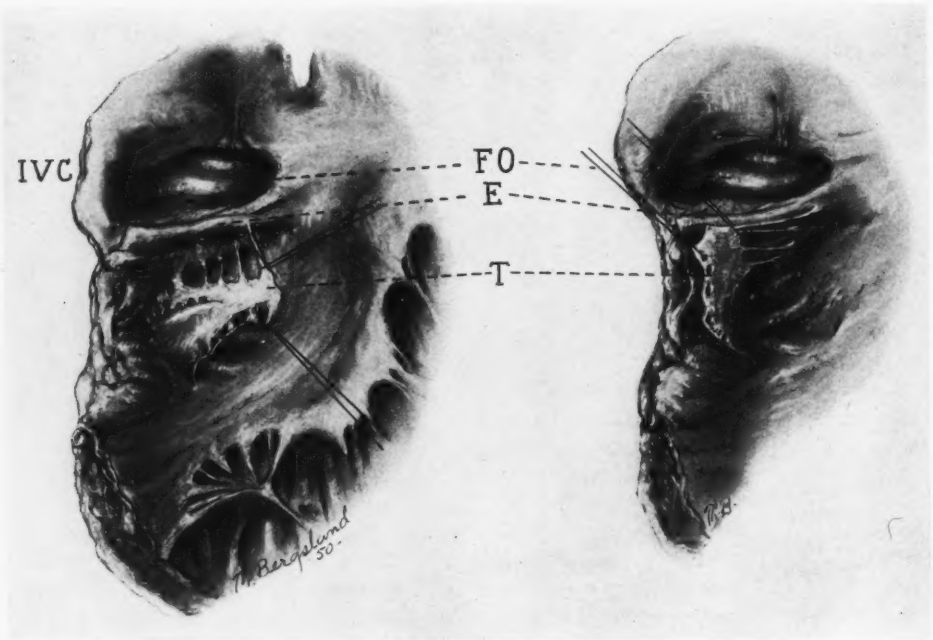


FIG. 7. A-10075. Thebesian valve is a complex membrane with multiple fenestrations and strands. The maximum diameter of the coronary orifice was 3 mm.

orifice. There was a common origin at the right rim of the orifice, and two insertions in the lower left rim (10 o'clock, and 3 and 5 o'clock respectively).

(3) In 30.7 per cent (46 cases), the thebesian valve was large, and also consisted of a broad, thin, transparent membrane, forming a virtually complete cover for the coronary orifice (figs. 5 to 7). The attached edge also was in the right inferior region of the coronary orifice, and the free edge was directed anteriorly, cephalad and toward the left. In this group, the thebesian valve could function as a true valve. The height of the valve averaged 7.1 mm. with a range of 5 to 12 mm. In 10 cases there were single or multiple fenestrations scattered throughout the membrane. The fenestrations usually were less than 2 mm. in diameter. In 1 unusual case, the fenestrations were situated around the total circumference of the valve (fig. 6). Because the thebesian valve in these cases covered the coronary orifice, catheterization would have been extremely difficult. However, if the catheter made an oblique angle, and if the thebesian valve were distended maximally into the atrium, the orifice might conceivably be negotiated. The maximum orifice in these circumstances has an average diameter of 8.6 mm.

(4) In 8 cases (5.3 per cent), the thebesian valve was represented by a thin fibrous bar across the coronary orifice. Usually the bar was transversely oriented, measured 3 to 5 mm. in width, and was also accompanied by several thin strands and threads (fig. 8).

(5) In 8 cases (5.3 per cent), the thebesian valve consisted of fine strands only; in 1 case, the strands formed a network in the orifice of the coronary sinus (figs. 9, 10). In 1 case, several fine threads originated at the apex of a small triangular membrane in the inferior margin of the orifice of the sinus.

(6) In 9 cases (6.0 per cent) there was a common valve for the caval and coronary sinus orifices (fig. 11). The thebesian valve was continuous with the eustachian valve. In 3 cases the thebesian valve was crescentic, in 3 semilunar, and in 3 cases the thebesian valve consisted of a delicate network. In 2 of the last 3 cases this comprised part of a Chiari's network.

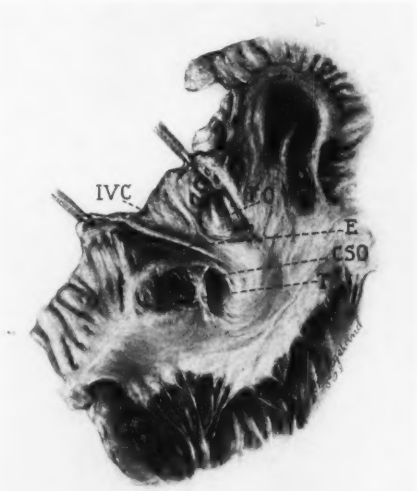


FIG. 8. A—9995. Thebesian valve consists of a transverse bar (4 mm. in width) and several strands.

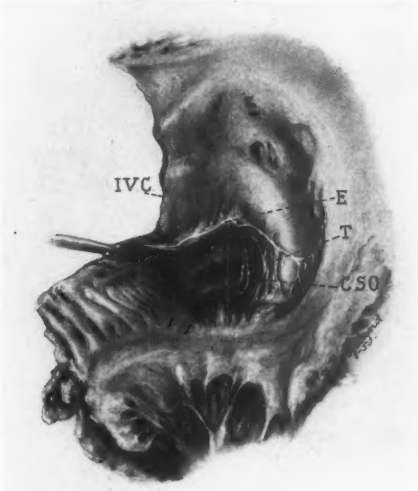


FIG. 9. A—9990. Thebesian valve consists of strands which are continuous with the eustachian valve.

Variations in the Diameter of the Orifice of the Coronary Sinus. There is a considerable range in the diameter of the orifice of the coronary sinus. The maximum diameter depends upon the presence and configuration of the thebesian valve, and is related to the presence of diffuse cardiac hypertrophy and dilatation, and clinical congestive heart failure. The maximum diameter in those cases where the thebesian valve was absent had an average value of 11.1 mm., with a range of 7 to 19 mm.; the average diameter in the group with small crescentic folds was 9.9 mm., with range of 7 to 15; and the mean maximum diameter of the group with large semilunar folds was 8.6 mm. with a range of 5 to 13 mm. Thus, the mean maximum diameter varied inversely with the extent of the thebesian valve.

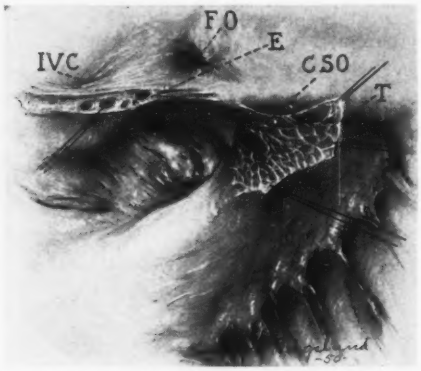


FIG. 10. A—3812 P. Thebesian valve consists of a network and the eustachian valve is a fenestrated membrane.

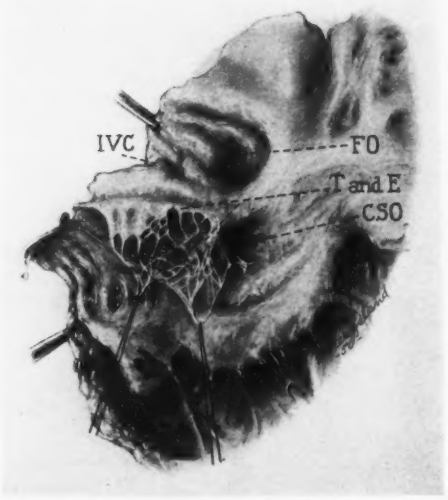


FIG. 11. A—10005. The thebesian and eustachian valves consist of networks which are continuous with each other and a Chiari's network.

In table 2, the relationship between the presence of congestive heart failure and the size of the maximum diameter is illustrated.

TABLE 2.—*Relation of Heart Failure to the Size of the Orifice of the Coronary Sinus*

	Non-failure	Failure	Total Group
Number of Cases	114	36	150
Mean Heart Weight (Gm.)	393	568	434
Range of Heart Weight (Gm.)	180–730	240–1040	180–1040
Mean Maximum Diameter of Orifice of Coronary Sinus (mm.)	9.27	10.7	9.63
S. D. of Mean Diameter of C. S.	2.23	2.33	2.2
Range of Mean Diameter of C. S.	3–15	6–19	3–19

TABLE 3.—*Relation of Heart Failure and Heart Weight*

	400 Gm. and Above	Less than 400 Gm.	Wt. not known
Heart Failure	33	2	1
No Heart Failure	55	57	2
Per cent Failure	37.5	3.4	
Mean Maximum Diameter of Orifice of Coronary Sinus (mm.)	10.3	8.78	

The hearts which had failed tended to have larger coronary orifices. This would imply that the dilatation of the heart, including the right atrium, which occurs in congestive heart failure was accompanied by a dilatation of the coronary sinus orifice. However, another, and probably more important, factor must be considered: the relation of the heart weight to the size of the coronary orifice. In table 3, it is clearly shown that a larger per cent of hearts 400 Gm. or more in weight failed than those

less than 400 Gm. The mean maximum diameter of the orifice of the coronary sinus is greater in the hearts above 400 Gm. Furthermore, in the group with hearts over 400 Gm., the mean diameter was greater in those who failed than those who did not: 10.6 and 9.9 respectively. Although the differences are small, we believe that there is a trend for the larger hearts, and hence those which are more likely to fail, to have larger orifices of the coronary sinus.

Variations of the Eustachian Valve. The eustachian valve (valve of the inferior vena cava) varies considerably also. The eustachian valve is usually a muscular and membranous fold in the right atrium which arises in the region of the lower extremity of the crista terminalis, and extends inferomedially to a point below the fossa ovalis, where fusion occurs with the muscular ridge of the sinus septum.

The valve of the inferior vena cava showed the same types of variations described by others[8, 9]: absent, fibrous ridge, simple intact or fenestrated membrane, cobweb network of threads, Chiari's network, and common eustachian and thebesian valves. In 75 per cent of the cases the eustachian valve was a simple valve whose depth was less than 10 mm.[8] In the present study, we have been more interested in the structure of the medial extremity of the eustachian valve than in the variations of the valve leaflet, since the former is more important in determining the feasibility of catheterizing the coronary sinus. We recall that the orifice of the coronary sinus is located directly below and medial to this portion of the valve of the inferior vena cava. In the subsequent discussion we shall refer to this portion as the eustachian ridge.

In 32 cases (21.3 per cent) the eustachian valve was absent and the eustachian ridge was smooth and nonprominent. In 10 of the 32 cases the thebesian valve was also absent. The approach to the orifice of the coronary sinus in these cases would be unimpeded.

In 71 cases (47.3 per cent) the eustachian ridge was firm, fibrous, and measured in depth from 1 to 6 mm., with an average of 2.4 mm. In 38 cases (25.4 per cent) the ridge was membranous, and tended to be wider, with a mean of 3.5 mm., and a range of 1 to 8 mm. In 8 cases, there was a large fenestrated membrane in this region, overhanging the coronary ostium. The maximum width in the region of the coronary sinus was 21 mm. Since the interstices measure 1 to 2 mm., a cardiac catheter conceivably might become entangled therein. In 1 case there was an extensive network continuous with a large fenestrated fold of the eustachian valve, thebesian valve and Chiari's network.

Chiari's Network. In 5 cases, a Chiari's network was present, fulfilling the following requirements: a network of fine or coarse fibers in the right atrium; its attachments extending from the interatrial septum or the upper portion of the crista terminalis to the thebesian and the eustachian valves or to the region of the orifices of the coronary sinus and the inferior vena cava. In 2 cases, both the thebesian and eustachian valves were absent. In 2 cases the thebesian valve was a large network and continuous with a similarly fenestrated eustachian membrane. Each connected to the Chiari's network. In 1 case the thebesian valve was crescentic and the eustachian a narrow membrane (3 mm. deep). In none of these cases were there thrombi lodged in the fibers of the network.[11]

Discussion

Relation of Anatomic Variations of Venous Valves of Right Atrium to Ease of Catheterization of Coronary Sinus in Man

Only 25 per cent of deliberate attempts to catheterize the coronary sinus in man are successful[7] while inadvertent catheterization of the coronary sinus may occur in 16 per cent of routine consecutive right heart catheterization.[15] The failures have been ascribed to the presence of an elevated eustachian ridge present in man, but not in dogs.[6, 7] Our present study however clarifies some of the above difficulties, by focusing attention on the variations of both the eustachian ridge and thebesian valves. The latter we believe are more important, since the eustachian ridge is broad and overhangs the orifice of the coronary sinus in less than 25 per cent of the cases. In 75 per cent of all cases, the eustachian ridge measures

less than 10 mm. in height. The technic by which the tip of the catheter can be maneuvered under fluoroscopic control to a position medial (left) to the medial extremity of the eustachian valve and the orifice of the coronary sinus has been developed by Goodale and associates.[1, 2]

Upon reviewing the anatomic features of the eustachian ridge, it becomes evident that a high per cent of failures must be attributed to other causes, namely, variations of the thebesian valve. In our series, we believe that even though the tip of a catheter could be placed (under fluoroscopic control) into the region of the orifice of the coronary sinus,

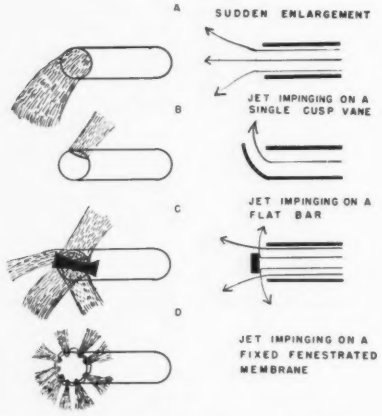


FIG. 12. Effect of variations of thebesian valve on mixing on coronary venous blood. Discussed in text.

intubation would have been impossible in 37 cases (24.7 per cent) because the coronary orifice was completely covered by a membrane. On the other hand, intubation definitely would have been successful in those cases where the thebesian valve was entirely absent (14.7 per cent), or small, crescentic and covering less than half of the coronary orifice (38 per cent), a total of 52.7 per cent. In the remainder (22.6 per cent), successful catheterization would have required dextrous manipulation to enter obliquely a small orifice in the cases with large membranes or bars and strands, and to avoid becoming entangled in networks. Catheterization of the last group would probably be purely fortuitous. Since this study was completed, Levine and Goodale[6] have reported success in catheterizing the human coronary venous system in 17 of 30 patients (56.7 per cent). They attribute their failures to prominence of the eustachian ridge, and state that the thebesian valve has never appeared to interfere with coronary sinus intubation in their patients. However, in about one-third of all human hearts, the coronary sinus is covered by a large membrane, as shown by the present study, and the observations of Wright, Anson and Cleveland.[8]

Dispersing or Mixing Effect of the Thebesian Valve

The variations of the thebesian valve may explain the great variations in oxygen content in the blood obtained at different levels in the right atrium and right ventricle. Coronary sinus blood has a low oxygen content, from 3 to 7 volumes per cent[2] while mixed caval blood contains normally 12 to 15 volumes per cent. If the poorly saturated coronary venous blood enters the right atrium in a stream, as it would do in the complete absence of a thebesian valve, poor mixing in the right atrium is likely, with streamline flow into the right ventricle. On the other hand, if a large fold is present, the coronary venous blood would be deflected to the left, behaving like a jet directed against a single cusp vane or curved fixed vane (fig. 12).[13] If fenestrations are present, the blood would be sprayed into the right atrium just above the tricuspid valve (fig. 12). In the cases with transverse or vertical bars, the mixing of blood would resemble a jet impinging on a flat plate (fig. 12). Since coronary venous flow is greatest during ventricular systole the spraying action would be greatest at this time. The mean velocity of coronary venous blood passing through the orifice of the coronary sinus can be roughly estimated to be about 3 cm. per second, if one assumes (1) the cardiac output is 5 liters per minute; (2) coronary arterial flow is 5 per cent cardiac output; (3) the coronary sinus carries 60 per cent of the total coronary flow; (4) the

mean diameter of the coronary sinus is 10 mm. (area 0.7854 square cm). The differences in pressure in the right atrium and the coronary sinus have not been considered in the above calculations. The velocity would likewise be altered, increasing particularly where the orifice is significantly smaller than the sinus (as in the case of a membrane partially covering the coronary sinus).

Summary

The anatomic variations of the orifice of the coronary sinus were studied in 150 formalin preserved hearts. There were six main types of variation of the valve of the coronary sinus (thebesian valve): (1) absent in 14.7 per cent, (2) small and crescentic in 38 per cent, (3) large and covering the entire orifice of the coronary sinus in 30.7 per cent, (4) bars and bands in 5.3 per cent, (5) threads and networks in 5.3 per cent, and (6) common eustachian and thebesian valves in 6.0 per cent. In one case, the coronary vein emptied into both atria by way of separate orifices. A true Chiari's network was found in 5 hearts.

The mean maximum diameter of the orifice of the coronary sinus was 9.6 mm., with standard deviation 2.2 mm. The size of the orifice was definitely related to the configuration of the thebesian valve, heart weight and the presence of congestive heart failure.

The anatomic variations of the orifice of the coronary sinus were considered to be important from the standpoint of catheterization, mixing of coronary venous blood, and, in one case with two orifices, from the standpoint of benefit from the Beck operation (aorta–coronary sinus anastomosis).

The difficulties encountered in the catheterization of the human coronary sinus are probably due to obstruction of the orifice by large membranes, bars and networks in 47.3 per cent of the cases and by a broad overhanging eustachian ridge in less than 25 per cent of the cases. Considering the anatomic variations of the venous valves of the right atrium in this series, catheterization of the human coronary sinus should be possible in a maximum of 75 per cent of the cases and very unlikely in the remainder.

References

[1] Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., and Banfield, W. G., Jr.: Coronary sinus catheterization for studying coronary blood flow and myocardial metabolism. Am. J. Physiol. **152:** 340, 1948.

[2] —, —, and Banfield, W. G., Jr.: Catheterization of the coronary sinus. Am. J. M. Sc. **214:** 695, 1947.

[3] Eckenhoff, J. E., Hafkenschiel, J. H., Foltz, E. L., and Driver, R. L.: Influence of hypotension on coronary blood flow, cardiac work and cardiac efficiency. Am. J. Physiol. **152:** 545, 1948.

[4] —, —, Harmel, M. H., Goodale, W. T., Lubin, M., Bing, R. J., and Kety, S. S.: Measurement of coronary blood flow by the nitrous oxide method. Am. J. Physiol. **152:** 356, 1948.

[5] Hackel, D. B., Goodale, W. T., Johnson, R. P.: Myocardial metabolism in thiamine-deficient dogs studied by intravenous catheterization of the coronary sinus. Federation Proc. **8:** 59, 1949.

[6] Levine, H. D., and Goodale, W. T.: Studies in intracardiac electrography in man. IV. The potential variations in the coronary venous system. Circulation **2:** 48, 1950.

[7] Bing, R. J., Hammond, N. M., Handelsman, J. C., Powers, S. R., Spencer, F. C., Eckenhoff, J. E., Goodale, W. T., Hafkenschiel, J. H., and Kety, S. S.: The measurement of coronary blood flow, oxygen consumption, and efficiency of the left ventricle in man. Am. Heart J. **38:** 1, 1949.

[8] Wright, R. R., Anson, B. J., and Cleveland, H. C.: The vestigial valves and the interatrial foramen of the adult human heart. Anat. Record **100:** 331, 1948.

[9] Yater, W. M.: Variations and anomalies of the venous valves of the right atrium of the human heart. Arch. Path. **7:** 418, 1929.

[10] Chiari, H.: Über Netzbildungen im rechten Vorhofe des Herzens. Beitr. z. path. anat. u.z. allg. path. **22:** 1, 1897.

[11] Orbison, J. L.: Thrombosis of anomalous chordae in the right atrium (Chiari's network). Am. Heart J. **37:** 119, 1949.

[12] Beck, C. S., Stanton, E., Batiuchok, W., and Leiter, E.: Revascularization of the heart by grafting a systemic artery or a new branch from the aorta into the coronary sinus. J. A. M. A. **137:** 436, 1948.

[13] King, H. W., and Wisler, C. O.: Hydraulics, ed. 2, revised. New York, John Wiley and Sons, 1927.

[14] Wartman, W. B., and Hellerstein, H. K.: The incidence of heart disease in 2,000 consecutive autopsies. Ann. Int. Med. **28:** 41, 1948.

[15] Culbertson, J. W., Halperin, M. H., and Wilkins, R. W.: Catheterization of the coronary sinus in man. Am. Heart J. **37:** 942, 1949.

Pathology of the Pulmonary Vascular Tree

III. The Structure of the Intrapulmonary Arteries in Cor Triloculare Biatriatum with Subaortic Stenosis

By JESSE E. EDWARDS, M.D., AND WILLIAM B. CHAMBERLIN, JR., M.D.

The pulmonary vessels in 2 cases of cor triloculare with subaortic stenosis are compared. Each showed medial hypertrophy of the muscular arteries of the lungs. In 1 case concerning an 8 year old boy this class of vessels showed, in addition, severe intimal fibrosis. The arterioles were normal.

It is emphasized that the changes in the pulmonary arteries are similar to those seen in the Eisenmenger complex, in coarctation of the aorta proximal to a patent ductus arteriosus and in the normal fetus. These conditions, though anatomically different from each other and from cor triloculare with subaortic stenosis, are functionally alike in that there is in each a common ventricular ejectile force for the pulmonary and the systemic circulations in the absence of stenosis in the major arterial pathways to the lungs.

It is suggested that in cor triloculare biatriatum with subaortic stenosis, the structure of the pulmonary muscular arteries is, and that their function seems, similar to that of the fetus. The changes in the case of the malformation may be considered a carry-over from fetal life.

THAT under certain circumstances the pulmonary vessels play an active role in governing the distribution of blood ejected by the heart has been suggested by studies on the Eisenmenger complex,[1, 2] on coarctation of the aorta in which coarctation lies proximal to the aortic entrance of a patent ductus arteriosus,[3, 4] and on the Taussig-Bing complex.[5] In some respects the circulation after birth in these conditions resembles the circulation in the normal fetus before birth. This is so because there is a common ventricular ejectile force for both the systemic and pulmonary circulations in the absence of stenosis in the major arterial pathways to the lungs (fig. 1*a*). It has been suggested for the normal fetus that that proportion of the blood leaving the pulmonary trunk which goes to the lungs on one hand, and through the ductus arteriosus to the descending aorta on the other, is governed, in part at least, by the caliber of the intrapulmonary arteries. In the fetus the intrapulmonary arteries characteristically have a thick wall and a narrow lumen.[6] In the subject to be discussed in this paper, namely, cor triloculare biatriatum with subaortic stenosis, there is a similarity with the postnatal circulation characteristic of the Eisenmenger complex, of coarctation of the aorta proximal to a patent ductus arteriosus, of the Taussig-Bing complex, and of the circulation of the normal fetus. In this condition, there is a common ventricle. The pulmonary trunk and its valvular orifice are wide, while the aorta is narrow. Of particular significance is the fact that in the common ventricle there is a narrow tract through which blood must pass on its way to the aorta. Under these circumstances, were the pulmonary vessels to function as in the normal postnatal state and the resistance to pulmonary flow be low, there would be a preponderance of pulmonary blood flow and a deficiency of systemic flow. Systemic blood pressure could not be built up.[7] Life probably would fail at an early age.

The 2 cases of cor triloculare biatriatum with subaortic stenosis which will be discussed in this paper concerned patients who lived for six and eight years respectively after birth. In these cases the pulmonary muscular arteries were structurally different from the normal at this age but resembled the pulmonary muscular arteries of the normal fetus and of patients with the Eisenmenger complex and of patients with coarctation proximal to a patent ductus arteriosus. The thick media and relatively narrow lumen of these vessels seem to represent the anatomic expression of the high levels of

From the Mayo Clinic, Rochester, Minn., and St. Alexis Hospital, Cleveland, Ohio.

resistance to pulmonary blood flow which is assumed to have existed. In 1 of the 2 cases here discussed, clinical observations were made by Dr. J. Carlton Ernstene of the Cleveland Clinic, who kindly supplied the clinical data to us. Necropsy was performed on this patient by one of us (Chamberlin). The other case was described by Dr. M. J. Greenberg.[8] From the published account it is apparent that the malformation of the heart in Dr. Greenberg's case was like that in the case in which the necropsy was performed by one of us and which will be reported here. Dr. Greenberg kindly submitted to us an adequate amount of pulmonary tissue from his case, and from this tissue we prepared sections.

Greenberg's case concerned a boy who was 6 years of age at the time of death. When the patient was seen at the age of 5½ years he had been having severe attacks of bronchitis and on exertion would become dyspneic but not severely cyanotic. When slightly more than 6 years of age the boy contracted a cold and his condition deteriorated rapidly. He was dyspneic, orthopneic and cyanotic. At necropsy the changes of congestive cardiac failure as well as of pulmonary congestion were found. The heart was similar to that to be described in our case and in addition the ductus arteriosus was closed by a thrombus which seemed to be about 2 months of age.

Microscopically the pulmonary tissue in Greenberg's case revealed a picture of congestion and edema. There were striking changes in the intrapulmonary muscular arteries. As contrasted to the normal appearance of this class of vessels, the walls were thickened by having a thick media and the lumen was correspondingly narrowed (figs. 2*a* and *b*). None of the muscular arteries showed intimal fibrous thickening. The internal elastic lamina of these arteries was thick and wavy.

The elastic layers of the elastic pulmonary arteries were thick. A rare vessel of this class

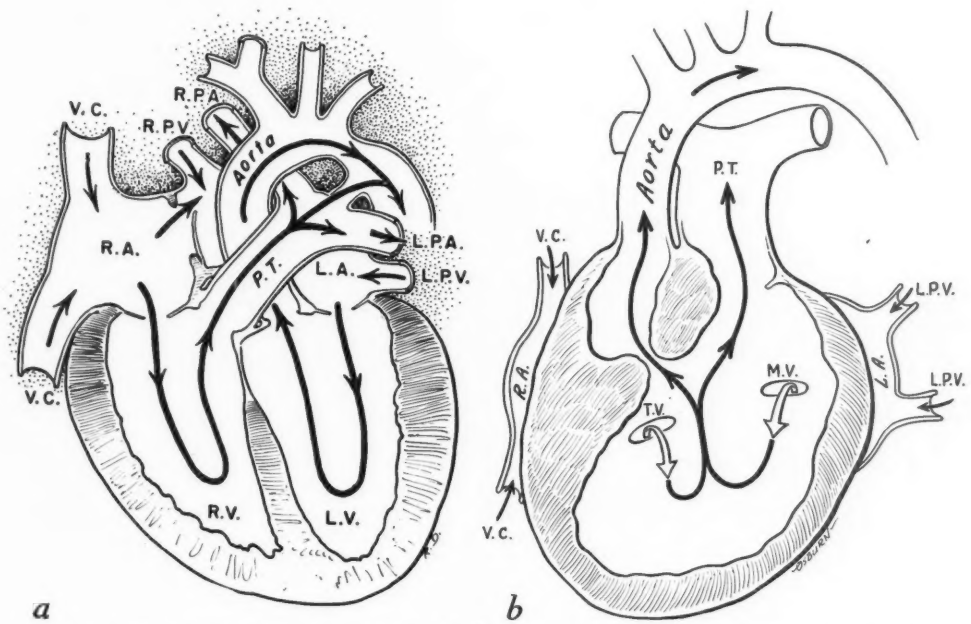


FIG. 1*a*. Normal fetal circulation. The right ventricle supplies blood to the lungs and to the descending aorta. *b*. Cor triloculare with subaortic stenosis. As in the normal fetal circulation there is a common ventricular ejectile force for blood to the lungs and to the systemic circulation without pulmonary stenosis.

showed fibrous intimal thickening. Throughout the pulmonary tissue the arterioles were normal.

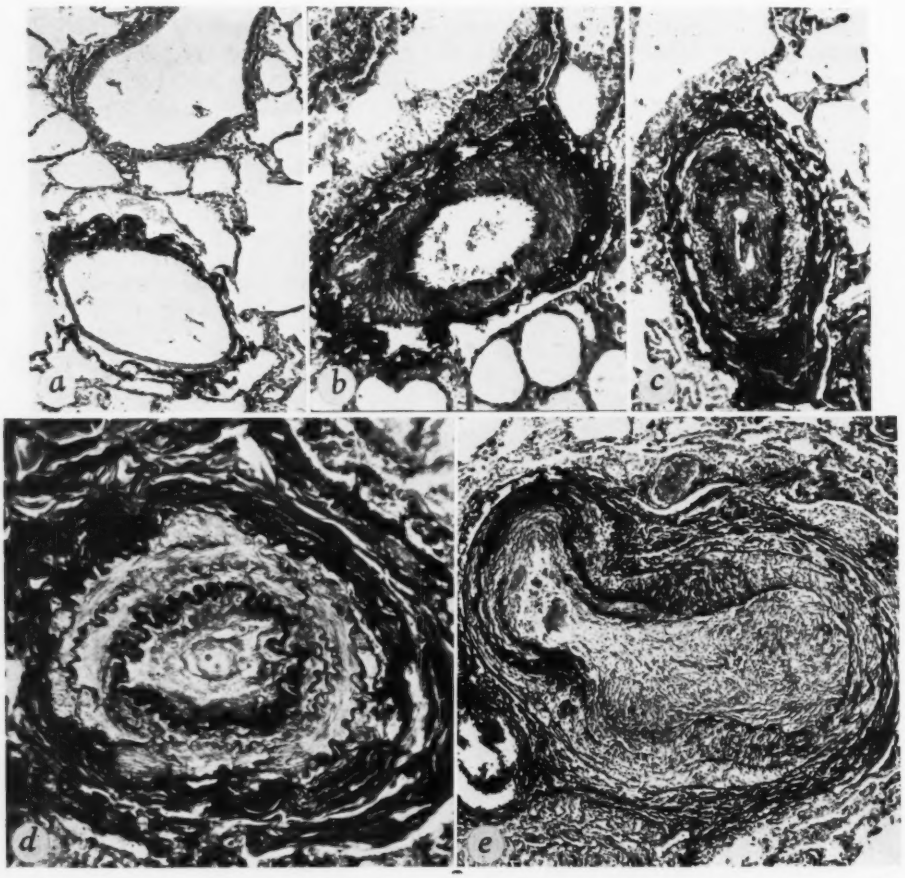


FIG. 2. Photomicrographs of pulmonary muscular arteries stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain. *a*. Normal muscular artery from a girl 7 years of age. As is normal at this age, the wall is thin and the lumen wide (× 75). *b*. From Greenberg's case. In contrast to the normal illustrated in *a*, the vessel shows a thickly muscular media and a relatively narrow lumen (× 75). *c*. From our case of cor triloculare biatriatum. Like the picture in Greenberg's case illustrated in *b*, the media is thickly muscular. Additionally there is superimposed intimal fibrous thickening (× 75). *d*. From our case. A muscular pulmonary artery shows a prominent internal elastic membrane and a thick media. Superimposed acellular nonvascular fibrous tissue accentuates the luminal narrowing (× 200). *e*. From our case. There is a break in the internal elastic membrane, focal atrophy of the media and aneurysmal dilatation of the vessel. An organized thrombus lies in the lumen (× 65).

The case in which necropsy was performed by one of us is here reported.

REPORT OF CASE*

Clinical Features. The patient was a boy who died at the age of 8 years on April 23, 1949. Dr. Ernstene, who kindly made the clinical data available to us, observed the patient on several occasions during the period between July, 1946, and April, 1949. Cyanosis had been present constantly and there was moderate polycythemia. An erythrocyte count made in March, 1949, revealed 7.8 million cells per cu.

* This case was included in a clinical and pathologic analysis of 9 cases of cor triloculare.[9]

mm. of blood. There were 20 Gm. of hemoglobin per 100 cc. of blood.

The physical examination revealed cardiac enlargement of a considerable degree. There was regular rhythm. A loud systolic murmur associated with a thrill was present in the second and third left intercostal spaces adjacent to the sternum. Roentgenoscopy confirmed the clinical suspicion of cardiac enlargement and suggested that there was right ventricular enlargement particularly. The pulmonary window appeared clear. The pulmonary arteries on each side were enlarged but there was no so-called hilar dance.

The electrocardiogram showed sinus tachycardia. There was evidence of marked right axis deviation and prominent P waves in standard leads II and III. The RS-T segments were depressed in leads II, III and aV_F. There were diphasic R waves in leads II, III, V_1 and V_2. The patient died at home.

Postmortem Findings. The necropsy, aside from revealing an infarct of the spleen, passive congestion of the liver, and edema of the legs, was particularly interesting as regards the heart and lungs.

The heart was tremendously enlarged. It was not weighed since it was desired to retain the connections of the heart and the lungs. It was estimated, however, that the heart weighed approximately 650 Gm. The venous connections with the heart were normal and there was a complete atrial septum separating the left and right atria. These chambers communicated by means of their respective atrioventricular valves with a large ventricular cavity representing a common ventricle. The great vessels were transposed, the aorta lying anterior and parallel to the pulmonary trunk. The pulmonary trunk, which was wide, measuring 2.5 cm. in diameter, and thick-walled, communicated freely with the outflow portion of the common ventricle. The aorta was narrower than the pulmonary trunk. In its ascending portion it measured 1.5 cm. in diameter. It communicated with a narrow pocket in the anterior aspect of the outflow portion of the common ventricle. A narrow tract measuring 1.4 cm. in diameter connected the main part of the common ventricle with the pocket that in turn communicated with the aorta. The ductus arteriosus was closed. There was moderate narrowing of the aorta proximal to the ligamentum arteriosum but no true coarctation. Except for a moderate degree of fibrous thickening of the pulmonary cusps, all the valves were normal. The coronary arteries arose from the aorta.

Grossly the lungs were divided into the usual number of lobes and were normally crepitant in their entirety. The cut surfaces of the lungs were pink and from them no excessive amount of blood exuded. The brain was normal.

It is evident from the cardiovascular arrangements as portrayed in figure 1*b* that all of the incoming blood, both venous and arterial, mixed in the common ventricle. There was no barrier between the common ventricle and the pulmonary trunk. In contrast, however, blood which flowed to the aorta had to pass from the main part of the common ventricle through a narrow channel leading to the pocket with which the aorta communicated. This narrow channel must have represented a barrier to the flow of blood to the systemic circulation.

Microscopically the pulmonary tissue from each of the lobes was similar in appearance. In some respects the changes were like those in Greenberg's case while in other respects the appearances were different. There was no congestion or edema of the lungs. The muscular arteries universally showed a thick media and a thick, wavy internal elastic membrane exactly as was observed in Greenberg's case. In striking contrast, however, marked intimal fibrous thickening was superimposed upon the medial changes of the muscular arteries. At times this change was responsible for almost complete obliteration of the lumen of this class of vessel (figs. 2*c* and *d*). As in Greenberg's case the elastic lamina of the elastic arteries was thick and the arterioles were normal.

The fibrous tissue which caused thickening of the intima of the muscular arteries had a tendency to be layed down in concentric layers. There was no vascularity of this tissue, nor did it contain any pigmented macrophages.

A rare large muscular artery showed focal interruption of the internal elastic lamina and atrophy of the media. This, at times, was associated with aneurysmal dilatation of the artery at the involved level and the lumen contained vascular fibrous tissue consistent with organized thrombus (fig. 2*e*).

The case here reported is an example of the congenital malformation known as cor triloculare biatriatum. Since the internal structure of the common ventricle in this condition may vary and since the narrow channel in the subaortic portion of the outflow tract is not constantly present,[10] we are of the opinion that the additional term "subaortic stenosis" should modify the principal diagnosis in this case. This suggestion is made with the realization that the modifying term subaortic stenosis as employed here is not to be confused with entity known as subaortic stenosis. In the latter entity there is ordinarily complete separation of the two ventricles from each other and the problems to the patient are simply related to obstruction in the outflow tract of the left ventricle.

The circulatory characteristic of our case may be defined as one in which there is a common ejectile force for the pulmonary and systemic circulations in the absence of stenosis in the major arterial pathways to the lungs (fig. 1*b*). In this regard the circulatory system

in this malformation functionally is like the cardiovascular system of the normal fetus and like those in individuals with malformations which anatomically differ from cor triloculare biatriatum with subaortic stenosis. These malformations include the Eisenmenger complex, coarctation of the aorta proximal to a patent ductus arteriosus, and persistent truncus arteriosus wherein there is a wide, though short, pulmonary trunk and the Taussig-Bing complex. Since in each of these conditions the right or a common ventricle supplies both circulations and since the systemic blood pressure is within normal limits, it is to be expected that the pulmonary blood pressure is similar to the systemic blood pressure. This has been established for patients with Eisenmenger complex,[1, 2] with coarctation proximal to a patent ductus arteriosus,[4] and with the Taussig-Bing complex,[5] and for the normal fetus.[11] In order for the pulmonary pressure to be elevated it is necessary that the resistance to flow within the pulmonary vascular bed be of magnitudes far exceeding normal, for the pulmonary resistance to be similar to the resistance to systemic flow.

In the fetus the muscular arteries with a thick wall and a narrow lumen seem to be the anatomic expression of such high resistance to pulmonary blood flow. In the Eisenmenger complex and in coarctation of the aorta proximal to a patent ductus, earlier work has demonstrated that the pulmonary muscular arteries are characterized by thick muscular medias and that the lumen of these vessels is relatively narrow.[3, 12, 13] These characteristics have not been considered to be abnormalities or malformations in themselves. On the contrary, they have been considered as representing a carry-over from fetal life into postnatal life. It has been considered that the thick-walled and narrow-lumened muscular arteries of the lungs play an important role in regulating the distribution of the blood which leaves the ventricular part of the heart to the lungs on one hand and to the systemic circulation on the other.

A similar function seems appropriately ascribed to the muscular arteries of the lungs in cor triloculare biatriatum with subaortic stenosis. In considering the functional and anatomic characteristics of our case and that of Greenberg here reviewed, it is correct to assume that pulmonary hypertension had existed. This seems to have depended upon the functional capacity of the myocardium on one hand and on the relatively narrow state of the pulmonary muscular arteries on the other. The medial hypertrophy of the pulmonary muscular arteries seems to be the essential factor in causing a state of high resistance of pulmonary flow since it existed in both our case and Greenberg's case. The appearance of severe intimal fibrous thickening in our case, in which the patient was older, seems to us to be a *result* of the pulmonary hypertension. It is apparent that once present the intimal changes would be responsible for even greater resistance to pulmonary flow and, if the myocardium continued capable, there would be an even greater degree of pulmonary hypertension.

The 2 cases taken together indicate that while the medial muscular changes may be the only ones for some time, intimal changes may eventually appear. The muscular changes may be responsible for a balanced distribution of the blood which leaves the heart.

The vessels with only this change may be flexible and of changing caliber. When intimal changes appear, the lumen of the vessel is further narrowed in a fixed nonflexible state. The intimal changes may be said to create a condition of intrapulmonary pulmonary stenosis. When this occurs it is possible that the balance of the circulation is upset, that whereas before the intimal changes made their appearance there was adequate pulmonary blood flow, after the changes become manifest there is a deficiency in pulmonary blood flow and a concomitant increase in magnitude of the venous-arterial shunt.

It has been seen that exactly the same type of anatomic changes develop in the Eisenmenger complex and it has been suggested that the appearance of intimal changes may be the factor which is responsible for the characteristic relatively late appearance of cyanosis in patients with the Eisenmenger complex.[13]

It is to be emphasized that the pulmonary arterioles in both of the cases being discussed were normal structurally. This indicates that the anatomic basis for increased resistance to

pulmonary blood flow cannot be placed at this level, but must be proximal to it at the level of the muscular arteries, the arteries which have been demonstrated to show organic changes.

The finding of pulmonary congestion in Greenberg's case and its absence in our case deserves some mention. In our case the severe narrowing of the pulmonary arteries caused not only by the basic medial thickening but also by the superimposed intimal fibrosis seems to have prevented great volumes of pulmonary blood flow. In Greenberg's case wherein the changes were exclusively medial, it is likely that, when the patient's cardiovascular system was in a balanced state, the lumen of the muscular arteries was even more narrow than at the time of death. The pronounced pulmonary congestion may mean that the flexible muscular arteries had lost some of their tone, that they had become wider, allowing an increased volume of pulmonary flow and leading to the existing pulmonary congestion and edema. In this regard it is possible that early death of certain patients with malformations characterized as having a common ejectile force for blood to the two circulations in the absence of pulmonary stenosis, may be understandable. If, in these conditions, the pulmonary muscular arteries go through a normal postnatal evolution the resistance to pulmonary flow may be below optimal level leading to excessive pulmonary blood flow and attendant congestion, edema, and hemorrhage.

The focal vessels in our case showing aneurysmal dilatation and organized thrombi deserve some mention. The changes in these vessels may represent the end stage of an acute arteritis and associated thrombosis. The presence of occasional thrombi in pulmonary arteries that constitute the seat of pulmonary hypertension for whatever cause is not uncommon; under these circumstances the arteries need not show evidence of inflammation. In certain instances of pulmonary hypertension acute pulmonary arteritis is observed, as in mitral stenosis[14] and in the Eisenmenger complex.[15] Whatever the basis for the arteritis under these circumstances, it is possible that in our case the occasional pulmonary vessels with aneurysms can be attributed to acute arteritis which had existed some time in the past.

Summary

The pulmonary vessels in 2 cases of cor triloculare with subaortic stenosis are compared. Each showed medial hypertrophy of the muscular arteries of the lungs. In 1 case concerning an 8 year old boy this class of vessels showed, in addition, severe intimal fibrosis. The arterioles were normal.

It is emphasized that the changes in the pulmonary arteries are similar to those seen in the Eisenmenger complex, in coarctation of the aorta proximal to a patent ductus arteriosus, and in the normal fetus. These conditions, though anatomically different from each other and from cor triloculare with subaortic stenosis, are functionally alike in that there is in each a common ventricular ejectile force for the pulmonary and the systemic circulations in the absence of stenosis in the major arterial pathways to the lungs.

The thick muscular pulmonary arteries are associated with a narrow lumen. This characteristic may be the anatomic expression of the increased resistance to pulmonary blood flow necessary for a balanced circulation in the presence of the malformation. It is suggested that the structure of the muscular arteries is similar and that the function seems similar to that of the fetus, and that the changes may be considered a carry-over from fetal life.

The intimal changes which developed in the muscular arteries in 1 case are considered as lesions secondary to the existing pulmonary hypertension. These cause the lumen of the involved vessels to be fixed in a stenotic state, and are probably responsible for a fall in pulmonary blood flow and a concomitant increase in the magnitude of the venous arterial shunt.

REFERENCES

[1] Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Physiological studies in congenital heart disease. III. Results obtained in five cases of Eisenmenger's complex. Bull. Johns Hopkins Hosp. **80**: 323, 1947.

[2] Lagerlöf, H., Mannheimer, E., and Werkö, L.: Heart catheterization in morbus caeruleus in Mannheimer's morbus caeruleus. An analysis

of 114 cases of congenital heart disease with cyanosis. Basel, S. Karger, 1949. Pp. 193–218.

[3] Edwards, J. E., Douglas, J. M., Burchell, H. B., and Christensen, N. A.: Pathology of intrapulmonary arteries and arterioles in coarctation of the aorta associated with patent ductus arteriosus. Am. Heart J. **38**: 205, 1949.

[4] Taylor, B. E., Knutson, J. R. B., Burchell, H. B., Daugherty, G. W., and Wood, E. H.: Patent ductus arteriosus associated with coarctation of the aorta: report of 2 case studies before and after surgical treatment. Proc. Staff Meet. Mayo Clin. **25**: 62, 1950.

[5] Taussig, Helen B., and Bing, R. J.: Complete transposition of the aorta and a levoposition of the pulmonary artery; clinical, physiological, and pathological findings. Am. Heart. J. **37**: 551, 1949.

[6] Civin, W. H., and Edwards, J. E.: The postnatal structural changes in the intrapulmonary arteries and arterioles. Arch. Path. In press.

[7] Hamilton, W. F., Winslow, J. A., and Hamilton, W. F., Jr.: Notes on a case of congenital heart disease with cyanotic episodes. J. Clin. Investigation **29**: 20, 1950.

[8] Greenberg, M. J.: An unusual congenital heart lesion; a case of functional *cor biatriatum triloculare* complicated by closure of a persistent ductus arteriosus. Guy's Hosp. Rep. **98**: 110, 1949.

[9] Rogers, H. M., and Edwards, J. E.: Cor triloculare biatriatum: a clinical and pathologic analysis of 9 cases. Am. Heart. J. In press.

[10] Shechter, F. R., and Greenspan, H. S.: Cor triloculare biatrium. J.A.M.A. **144**: 100, 1950.

[11] Hamilton, W. F., Woodbury, R. A., and Woods, E. B.: The relation between systemic and pulmonary blood pressures in the fetus. Am. J. Physiol. **119**: 206, 1937.

[12] Edwards, J. E.: Structural changes of the pulmonary vascular bed and their functional significance in congenital cardiac disease. Proc. Inst. Med. Chicago **18**: 134, 1950.

[13] Civin, W. H., and Edwards, J. E.: Pathology of the pulmonary vascular tree. I. A comparison of the intrapulmonary arteries in the Eisenmenger complex and in stenosis of ostium infundibuli associated with biventricular origin of the aorta. Circulation. **2**: 545, 1950.

[14] Parker, Frederic, Jr., and Weiss, Soma: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path. **12**: 573, 1936.

[15] Old, J. W., and Russell, W. O.: Necrotizing pulmonary arteritis occurring with congenital heart disease (Eisenmenger complex). Report of a case with necropsy. Am. J. Path. **26**: 789, 1950.

Physiologic Studies in Mitral Valvular Disease

By A. Draper, M.D., R. Heimbecker, M.D., R. Daley, M.D., D. Carroll, M.D., G. Mudd, M. D., R. Wells, M.D., W. Falholt, M.D., E. C. Andrus, M.D., and R. J. Bing, M.D.

Physiologic findings obtained by cardiac catheterization on 29 patients with mitral valvular disease are discussed. Cardiac outputs, intracardiac pulmonary arterial and pulmonary pressures are determined during rest and exercise. It is shown that the resting cardiac output is reduced in all patients with mitral disease and that exercise results either in a fall or a small increase in the minute volume of circulation. The pulmonary artery and capillary pressures are elevated with rest and rise further with exercise. A clear differentiation by physiologic means between mitral stenosis and mitral insufficiency is difficult. However, in patients with mitral insufficiency the resting cardiac output is lower, the arterial venous oxygen difference is higher and exercise causes a greater fall in the cardiac output. A comparison is made between the physiologic manifestations of mitral disease and myocardial failure: the residual volume of blood of the right ventricle is usually increased in patients with mitral disease and failure and in myocardial failure alone. However, the right ventricular residual volume is normal in mitral disease without evidence of myocardial failure. The pulmonary vascular resistance in mitral disease is usually elevated. It is demonstrated that in a number of patients the pulmonary vascular resistance is not fixed since it decreases during exercise or following valvulotomy of the mitral valve.

RECENT progress in the surgical treatment of mitral stenosis has renewed the interest in the hemodynamics of mitral disease.[1-3] Roentgenologic, clinical and pathologic studies have shown that mitral disease leads to engorgement of the pulmonary circulation with anatomic changes in the pulmonary vascular bed.[4-6] During the compensatory stage of the disease there is usually enlargement of the left auricle. If mitral insufficiency is present, there is also enlargement of the left ventricle. Dilatation and hypertrophy of the right ventricle are usually demonstrable in mitral disease. As the disease progresses. right-sided failure with engorgement of the systemic veins, swelling of the liver, edema and serous effusion make their appearance.

The hemodynamic events accompanying these clinical alterations have been studied by a series of authors The information obtained indicates that in mitral disease the pulmonary, arterial and right ventricular pressures are elevated.[7-10] There is a reduction in cardiac output and the resistance in the pulmonary vascular bed is increased.[7]

This paper sets forth the physiologic findings obtained by cardiac catheterization in 18 patients suffering from mitral stenosis and in 11 patients suffering from mitral stenosis and insufficiency referred to hereafter as "mitral insufficiency." The chief alterations in pulmonary hemodynamics and cardiac function will be described and their significance discussed. Where possible, the data will be correlated with the clinical manifestations of the disease. Pre- and postoperative catheterization studies in 3 patients will be presented.

Material and Method

Cardiac catheterization was performed in 29 patients with mitral valvular disease. The ages of these patients ranged from 16 to 50 years. Five were males and 24 were females. No patient at the time of catheterization had clinical evidence of valvular disease other than mitral. Criteria for the diagnosis of mitral stenosis or mitral insufficiency were taken from the recommendations of the New York Heart Association.[11]

Table 1 summarizes the clinical findings. Eleven patients who were classified as having "mitral insufficiency" had both a systolic murmur of moderate intensity at the apex and roentgenographic evidence of left ventricular enlargement. All 11 had fluoroscopic evidence of left auricular enlargement and 9 had right ventricular failure and auricular fibrilla-

From the Department of Surgery, Johns Hopkins Hospital and University, Baltimore, Md.

This work has been supported by the grants from the Commonwealth, Carolyn Rose Strauss and the Gulftex Foundations.

tion. Two (R. T. and C. C.) had episodes of acute pulmonary edema and 1 (C. C.) a history of hemoptysis. Three (F. P., B. Y. and C. C.) gave a history of systemic arterial embolism.

All 18 patients with mitral stenosis alone had characteristic apical diastolic murmurs. Ten had accentuated apical first sounds. Fifteen had fluoroscopic evidence of left auricular enlargement. Although 7 of the 18 patients had soft apical systolic murmurs, none had left ventricular enlargement. Five patients with mitral stenosis had right ventricular failure at the time of examination (J. C., F. J., R. R., M. C., M. H.). One (F. C.) developed failure two months, and another (F. M.) five weeks after examination. Seven (P. B., D. E., M. T., F. C., F. J., R. C., M. H.) had auricular fibrillation. Eight gave a history of definite episodes of acute pulmonary edema (J. C., M. T., F. C., S. R., R. S., W. W., R. R., M. H.), and 8 of hemoptysis (M. K., R. S., R. B., W. W., F. M., R. R., M. B., M. H.). Four

TABLE 1.—*Distribution of Clinical Findings*

	Mitral Stenosis (18 patients)	Mitral Insufficiency (11 patients)
Murmur—Diastolic	18	11
Systolic	10	11
Left Auricular Enlargement	15	11
Left Ventricular Enlargement	none	11
Right-sided Failure	5	9
Auricular Fibrillation	7	9
Pulmonary Edema	8	2
Hemoptysis	8	1
Embolic Phenomena	4	3

(P. B., F. C., R. C., M. H.) had had systolic embolic episodes.

Cardiac catheterization was performed in the usual manner. Right auricular, right ventricular, pulmonary artery pressures and pulmonary capillary pressures were recorded according to the methods outlined by Calazel and associates.[12] An indwelling needle (No. 20) was inserted into either the brachial or the femoral artery. After an interval of five minutes designed to reestablish basal conditions, simultaneous arterial and mixed venous blood samples were withdrawn over a period of one minute into oiled and heparinized syringes. At the same time expired air was collected in a Douglas bag. Pulmonary arterial pressures were usually recorded just before or after the collection of blood samples. Patients were then exercised by repeated flexion of the legs against a resistance. If the femoral artery contained an indwelling needle, one leg and one arm were exercised. Exercise was continued for approximately three minutes unless the patients became too tired. During the final minute of exercise, simultaneous pulmonary arterial, systemic arterial and expired air samples were collected. Pulmonary arterial, and pulmonary capillary pressures were recorded just before termination of the exercise. Right ventricular and right auricular pressures were usually obtained after the patient had regained basal conditions. Pressures were transduced with Statham strain gages and Hathaway galvanometers, and were optically recorded. The "zero" point for the pressures was obtained by placing the strain gages approximately 10 cm. above the back of the patient. Mean pressures were obtained by planimetric integration of the area under the pressure curves or by adding one-third of the pulse pressure to the diastolic pressure. Expired air samples were analyzed for carbon dioxide on the Haldane-Henderson apparatus and for oxygen on the Pauling apparatus. The total volume of expired air was measured with a wet test meter. All volumes were expressed as dry gas at 0 C. and 760 mm. pressure. Blood oxygen analyses were carried out according to the method of Van Slyke and Neill.[13] The cardiac output was calculated in accordance with the Fick principle.[14]

The residual volume of blood in the right ventricle was estimated by the injection of Evans blue into the right ventricle and by withdrawing blood containing the dye from the pulmonary artery.[15] The results obtained with this method on normal individuals and 8 patients with mitral stenosis will be described in a subsequent publication. In this report only brief reference will be made to the results obtained.

The pulmonary arteriolar resistance was obtained from the equation,[16]

$$\textit{Pulmonary Arteriolar Resistance} = \frac{\left(\textit{Mean Pulmonary Artery Pressure} - \textit{Mean Pulmonary Capillary Pressure}\right)}{\textit{Pulmonary Blood Flow}}$$

where arteriolar resistance is expressed as mm. Hg/L./min./M.^{2}, pressures are expressed as mm. Hg, and blood flow is expressed as L./min./M.^{2} Since in some patients pulmonary capillary pressures could not be obtained pre- and postoperatively, pulmonary vascular resistance was calculated by assuming a pulmonary capillary pressure of 35 mm. Hg. By using this maximal pulmonary capillary pressure minimal pulmonary resistances were obtained. In all patients in whom pulmonary capillary pressures were not recorded preoperatively, minimal preoperative values were compared with postoperative figures obtained by direct measurements.

Right ventricular work, expressed in kilogram meters per minute, was calculated from the formula of Starling[7]

$$\text{Right ventricular work} = \frac{\text{Mean Pulmonary Artery Pressure} \times \text{Cardiac Output} \times 13.6}{1000}$$

where pressure is expressed as mm. Hg. and output is expressed as L./min. With this formula the pressure energy alone was obtained. No allowance was made for velocity energy, since with increasing pulmonary vascular resistance most of the energy cost of the right ventricle is expended in the form of pressure energy.[18,19]

ment with those of Dexter.[7] Congestive failure may account for these low cardiac outputs, for 9 out of 11 patients who had mitral insufficiency had clinical signs of heart failure (table 1). Out of 6 patients with mitral stenosis who had cardiac indices of less than 2.0 L./min./M.^{2} 4 were clinically in failure at the time of examination. One developed failure five weeks later, and one two months later.

TABLE 2.—*Data on Oxygen Consumption, A-V Oxygen Difference, Cardiac Output, and Oxygen Equivalent of Patient with Mitral Stenosis*

Case	S.A.	Date	O_2 Cons.		A-V Diff.		Cardiac Output/M.^{2}		O_2 Cons./Liter Ventilation	
			Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.
J. C.	1.86	7/6/49	169	359	4.74	6.29	1.92	3.04	31.5	27.8
P. B.	1.71	10/19/49	209	296	3.86	4.79	3.18	3.64	35.0	27.6
P. H.	1.38	10/26/49	148	335	4.00	6.30	2.68	3.62	27.6	25.0
D. E.	1.88	11/7/49	250	338	6.13	6.97	2.17	2.59	30.5	24.8
M. T.	1.56	11/25/49	211	186	3.57	4.79	3.48	2.48	35.7	29.0
F. C.	1.54	1/5/50	126	308	5.53	7.50	1.49	2.66	26.5	26.9
M. K.	1.61	1/27/50	166	201	4.73	5.40	2.18	2.31	23.5	22.3
S. R.	1.56	2/6/50	175	247	3.43	5.47	3.25	2.88	33.0	33.0
R. S.	1.56	11/9/49	175	343	3.82	4.70	2.94	4.68	21.6	20.0
F. J.	1.33	1/25/50	134	142	6.69	7.71	1.57	1.35	17.8	21.0
R. B.	1.48	4/4/50	207	278	4.43	6.53	2.61	2.45	41.0	33.7
W. W.	1.98	4/5/50	208	344	3.80	5.37	2.77	3.24	48.4	42.9
R. C.	1.66	3/30/50	197	266	5.89	6.95	2.02	2.31	26.0	30.5
F. M.	1.54	4/12/50	176	221	6.12	7.73	1.87	1.86	32.8	32.2
W. S.	1.30	5/15/50	143	167	5.35	7.98	2.06	1.61	34.7	44.3
R. R.	1.55	5/25/50	179	161	5.09	6.33	2.28	1.65	37.4	18.6
M. B.	1.82	5/29/50	203	252	7.00	9.58	1.52	1.38	33.7	25.7
M. H.	1.67	6/19/50	197	270	6.24	8.34	1.89	1.94	30.2	37.3
Average			187	262	5.03	6.60	2.33	2.54	31.5	29.0

RESULTS

Table 2 shows that the cardiac output was significantly reduced in patients with mitral stenosis. This reduction was even more marked in patients with mitral insufficiency (table 3). It may be seen from table 2 that in mitral stenosis the resting cardiac output ranged from 1.49 liters per minute per square meter of body surface to 3.48 L./min./M.^{2} averaging 2.33 as compared with a normal figure of approximately 3.0.[20] Only 3 patients (P.B., M. T., S. R.) had normal values. In mitral insufficiency the cardiac output ranged from 0.85 to 2.50 (L./min./M.^{2}) with an average of only 1.92 (table 3). These results are in agree-

In 8 out of 18 patients with mitral stenosis, exercise resulted in a fall in cardiac output. However, there was an average increase of 9 per cent for the whole group (table 2). In 5 of 7 patients with mitral insufficiency exercise caused a fall in output, with an average decrease of 2.9 per cent (table 3). It has been pointed out that in failure a fall in cardiac output with exercise indicates that the resting output is the maximum that can be consistently maintained by the heart.[21, 22] It is not surprising therefore, that, if the resting output in these patients with frank myocardial failure is low, exercise causes a still further decrease. The part played by regurgitation of blood in

the diminution of the minute volume at rest and exercise may be of great significance. However, the volume of blood which enters the left auricle during ventricular systole cannot be calculated, using the Fick principle.

mitral stenosis at rest was slightly elevated (average 5.03 volumes per cent with a range from 3.43 to 7.00) (table 2). In mitral insufficiency the arteriovenous oxygen difference was markedly increased [average 5.75 volumes

TABLE 3.—*Data on Oxygen Consumption, A-V Oxygen Difference, Cardiac Output and Oxygen Equivalent of Patients with Mitral Insufficiency*

Case	S.A.	Date	O_2 Cons.		A-V Diff.		Cardiac Output/M.^{2}		O_2 Cons./L. Ventilation	
			Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.
F. P.	1.45	7/9/48	164		13.22		0.85		22.7	
R. T.	1.61	7/12/48	206		6.91		1.97		31.5	
V. A.	1.62	7/15/48	185		5.99		1.92		29.0	
B. Y.	1.42	12/22/48	158	196	6.29	8.09	1.76	1.70	21.0	14.0
W. M.	1.93	1/18/49	241	255	5.95	7.80	2.10	1.68	29.8	25.3
A. E.	1.49	3/4/49	161	183	4.25	6.52	2.50	1.89	24.1	19.9
J. N.	1.38	10/3/49	217		9.34		1.67		27.3	
C. C.	1.38	2/15/50	174	223	6.0	7.20	2.10	2.24	35.0	36.0
T. S.	1.73	2/9/50	188	272	6.12	9.62	1.78	1.64	28.2	30.5
[2]A. E.	1.49	3/15/50	191	251	7.20	11.09	1.78	1.52	26.6	20.2
G. H.	1.77	4/21/50	240	299	5.89	6.01	2.30	2.81	40.2	39.1
G. W.	1.57	4/6/50	226	306	7.28	8.28	1.97	2.36	33.4	30.0
Average			196	248	5.75	8.07	1.91	1.98	29.2	37.0

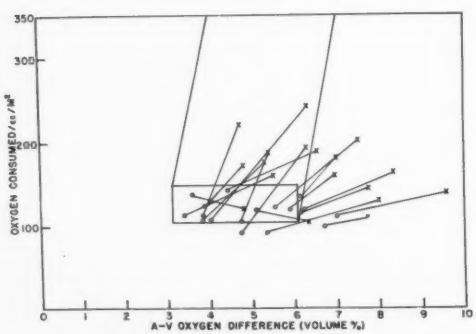


FIG. 1. The response of patients with mitral stenosis to exercise. The rectangle in the diagram includes resting normal values for oxygen consumption and arteriovenous oxygen difference. It may be seen that in most patients with mitral stenosis the A-V oxygen difference increases disproportionately to the oxygen consumption.

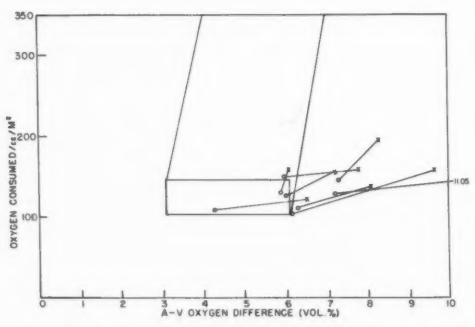


FIG. 2. A similar diagram for patients with mitral insufficiency. The increase in A-V oxygen difference during exercise is greater than in patients with mitral stenosis.

An examination of the figures for oxygen consumption and arteriovenous oxygen difference during rest and exercise (tables 2 and 3) illustrates that in both groups, but particularly in mitral insufficiency, the oxygen consumption increased slightly during exercise. The arteriovenous difference of patients with

per cent with a range from 4.25 to 7.28 (table 3)]. Exercise resulted in a significant increase in the arteriovenous oxygen difference in both groups, [average 6.60 volumes per cent with a range from 4.70 to 9.58 in mitral stenosis (table 2) and an average of 8.07 volumes per cent with a range of 6.01 to 11.09 in mitral insufficiency (table 3)]. This increase was out of proportion to the rise in oxygen consumption from rest to exercise. Figures 1 and 2 which

are adapted from Hickam and Cargill's paper[21] show the response of these patients to exercise. The rectangle in the diagram includes resting normal values for oxygen consumption and arteriovenous oxygen difference (figs. 1 and 2).

consumption (figs. 1 and 2). As a result the points obtained during exercise fell outside the normal area. The increase in arteriovenous oxygen difference was particularly great in mitral insufficiency.

TABLE 4.—*Pressures and Resistances and Right Ventricular Work in Patients with Mitral Stenosis*

Case		Pulmonary Capillary		Right Ventricle		Right Auricle		Pulmonary Artery		Pulmonary Arteriolar Resistance		Right Ventricular Work	
		Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.
J. C.	S/D			68/7				74/62	74/62	16*		3.21	6.15
	M					20		66	66				
P. B.	S/D							60/25		0.63*		2.74	1.71
	M							37					
P. H.	S/D	36/22		67/0		6/0		68/33	91/50	6.7		2.26	4.36
	M	27				3		45	64				
D. E.	S/D			67/2				79/44	100/78	11.5*		3.34	5.64
	M					3		60	85				
M. T.	S/D			60/0		10/0		60/29	70/35	1.15*		2.88	2.42
	M					5		39	46				
F. C.	S/D							84/46	108/65	20.8		1.97	4.47
	M	32	47			4		63	80				
M. K.	S/D	30/22	42/24	36/4		4/0		52/24	60/24	3.2	1.30	1.51	1.82
	M	26	33			2		33	36				
S. R.	S/D							49/27	58/29	0.62	1.74	2.34	2.38
	M	32	34			10		34	39				
F. J.	S/D	32/17		60/5		14/7		60/32	72/43	12.1	19.3		
	M	23	26			9		42	52				
R. S.	S/D	40/22		68/0		10/0		58/30	68/37	3.74		2.44	4.66
	M	28				4		39	47				
R. B.	S/D			62/6				63/34	48/22	9.4			
	M	19				6		44	31				
W. W.	S/D				33/3			31/31	39/38	2.9	0.62	2.84	3.99
	M	30	43					38	43				
R. C.	S/D	32/14		40/0				42/17	41/22	2.48			
	M	20						25	28				
F. M.	S/D				66/16			38/24	70/47	3.72	10.7	1.37	2.14
	M	28	35				10	35	55				
W. S.	S/D	24/17	22/13					32/20		2.4	6.2	0.87	0.74
	M	19	16					24	26				
R. R.	S/D	44/34						82/36	68/42	5.26		2.46	1.78
	M	39						51	51				
M. B.	S/D	66/31			127/96		30/23	97/45	138/91	8.56		2.34	3.66
	M	49					26	62	107				
M. H.	S/D	50/37	58/42		82/3	18/12	27/14	70/44	84/58	4.76	8.76	2.28	2.95
	M	44	50			15	20	53	67				
Average.....		29.8	35.5			7.4	16.5	43.9	54.4	6.44	7.63	2.19	2.96

* Minimal pulmonary resistance.

During exercise, the points should fall between the lines drawn from the rectangle to the top of the chart. It may be seen that in 18 patients with mitral stenosis and in 7 out of 8 with mitral insufficiency the A-V oxygen difference increased disproportionately to the oxygen

The oxygen consumption per liter of ventilation fell in 12 out of 18 patients with mitral stenosis and in 6 out of 8 patients with mitral insufficiency (tables 2 and 3). In normal persons oxygen consumption increases proportionately more than the minute volume of

ventilation during the standard exercise test and the ratio of oxygen consumed per liter of ventilation increases.[23, 24]

The pressure relationships within the pulmonary circulation are illustrated in tables 4 and 5. The mean pulmonary arterial pressure at rest was elevated in every patient of this series, averaging 43.9 mm. Hg, with a range of 24 to 66, in mitral stenosis, and 62.7 mm. Hg, with a range of 28 to 107, in mitral insufficiency (tables 4 and 5). Similar values were obtained by Dexter and Borden in patients with mitral stenosis.[7, 8] Lower values (21 mm. Hg) were found by Borden in patients with grade I or II functional incapacity.[8] Table 4 illustrates that exercise resulted in a rise in pulmonary arterial pressure in 14 out of 17 patients with mitral stenosis. Pulmonary artery pressures also rose in the 5 patients with mitral insufficiency in whom pressures were recorded during exercise (table 5).

The correlation between pulmonary arterial pressure and cardiac output is illustrated in figure 3 adapted from Hickam and Cargill's paper.[21] Normally, the capacity of the pulmonary vascular bed is so great that considerable changes in pulmonary flow can occur without any change in pulmonary artery pressure.[20] If, however, the pulmonary vascular resistance is fixed, an increase in pulmonary blood flow will result in a rise in pulmonary artery pressure. This was the case in the patients of this series. It is apparent, therefore, that in the majority of patients with mitral stenosis and mitral insufficiency, exercise resulted in a proportionately larger increase in pulmonary artery pressure than in pulmonary blood flow.

Because of the physiologic and clinical

TABLE 5.—*Pressures and Resistances and Right Ventricular Work in Patients with Mitral Insufficiency*

Case		Pulmonary Capillary		Right Auricle		Right Ventricle		Pulmonary Artery		Pulmonary Arteriolar Resistance		Right Ventricular Work	
		Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.
F. P.	S/D			12/10		70/22		81/58		36.5*		1.11	
	M			11		38		66					
R. T.	S/D			17/14		78/8		76/45		9.65*		2.33	
	M			15				54					
V. A.	S/D			28/15 (CS)									
	M			22									
B. Y.	S/D			33/23		135/23		133/60		27.8*		2.84	
	M			26				84					
W. M.	S/D					135/5		135/85		32.4*		5.67	
	M							103					
J. N.	S/D			20/9		100/48		146/88		37.1*		3.35	
	M			13				107					
C. C.	S/D	32/8	37/21	5/0		38/0	60/0	44/20	60/26	4.76	3.12	1.10	1.55
	M	18	30	2				28	37				
T. S.	S/D			10/5				55/17	62/42	6.74	12.81	1.17	1.90
	M	16	28	7				28	49				
A. E.	S/D			29/24			95/7/20	116/53	116/69	22.50		2.67	2.66
	M	34		26				74	86				
G. H.	S/D	44/15		21/12		77/11		72/36	88/57	13.04	6.76	3.05	4.34
	M	25	48	15				55	67				
G. W.	S/D				15/9	54/11		42/21	59/28	5.60	5.93	1.18	1.91
	M	18	24		12			28	38				
Average..... (Mean)		22.2	32.5					62.7	55.4	19.61	7.15	2.45	2.51

* Minimal pulmonary resistance.

importance of estimating left auricular and pulmonary vein pressures in patients with mitral valvular disease, pulmonary "capillary" pressures were recorded in 14 patients with mitral stenosis and in 5 patients with mitral insufficiency (tables 4 and 5). It has been shown that the height of this pressure bears a definite relationship to the height of the left

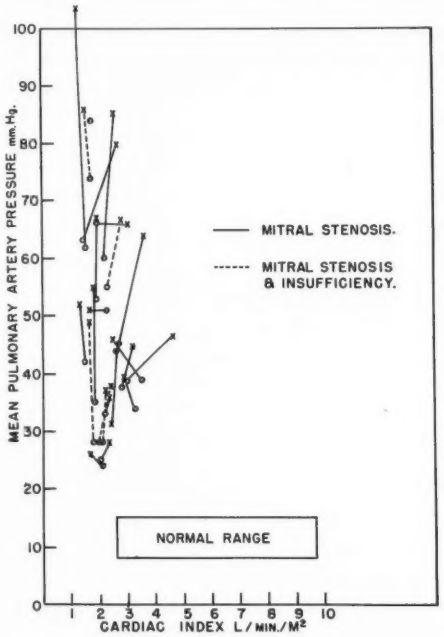


FIG. 3. The relationship of cardiac output to pulmonary pressure during exercise. It may be seen that exercise results in a proportionately larger increase in pulmonary artery pressure than in pulmonary blood flow. In normal man large increase in cardiac output does not result in an elevation of the pulmonary artery pressure.

auricular and pulmonary vein pressures.[12, 25] The average pulmonary "capillary" pressure in mitral stenosis was 29.8 mm. Hg with a range of 19 to 49 (table 4). In mitral insufficiency it averaged 22.2 mm. Hg, with a range of 16 to 34 (table 5). Exercise produced a rise in both groups; in mitral stenosis from 29.3 to 35.5 mm. Hg, and in mitral insufficiency from 19.3 to 32.5 mm. Hg. The generally accepted normal value is 10 mm. Hg or less.[12, 25]

Lagerlöf and Werko[26] have shown that the contour of the pulmonary "capillary" pressure tracing in patients with mitral stenosis or insufficiency differs from that recorded in normal individuals by a sharp rise. Figure 4 illustrates that in some patients of this series pulmonary "capillary" tracings have a series of sharp peaks which are even more conspicuous during exercise. Since simultaneous electrocardiograms or arterial pressures were not recorded, it is not possible to state whether these peaks occurred during the phase of auricular or ventricular contraction.

DISCUSSION

Findings reported in this paper show that the cardiac output of patients with mitral stenosis and insufficiency is decreased. Exercise results in either a small increase or a decrease in the minute volume of circulation. It is probable that cardiac failure contributed to the fall in cardiac output during exercise. This assumption is substantiated by the finding that of the 8 patients in whom the cardiac output fell 4 had clinical evidence of heart failure. It has been shown by a series of investigators that in severe failure the resting cardiac output is the maximal output that can be maintained by the heart.[21, 22] This is in line with Starling's concept that on increasing the filling load of the heart a point is reached where increased filling causes no further rise in output. From then on, any further elevation in load causes a decline in cardiac output.[17]

The decrease in cardiac output during rest and exercise is primarily the result of an increase in the arteriovenous oxygen difference (tables 2 and 3). This difference is particularly great in patients with mitral insufficiency (tables 2 and 3). During exercise the arteriovenous oxygen difference increases. The rise in A-V oxygen difference observed during exercise is proportionately greater than the increase in oxygen consumption (figs. 1 and 2). It must be assumed that mechanical factors such as limitation of flow or regurgitation of blood are at least partially responsible for the increased oxygen difference. However, here again, myocardial failure may play a major part.

The ratio of oxygen consumed per liter of ventilation fell in the majority of patients during exercise. A fall in this ratio is usually due to a disproportionate rise in the respiratory minute volume. The findings discussed above indicate that, in the patients of this series, the pulmonary blood flow and hence the oxygen consumption fail to increase in a normal fashion.

The pulmonary artery pressure at rest was elevated in every patient with mitral stenosis or mitral insufficiency. Usually, a further rise occurred with exercise (tables 4 and 5). This finding contrasts with that obtained in normal individuals, in whom a rise in cardiac output to three times its resting level produces no change in the pulmonary artery pressure.[20] The elevation of the pulmonary artery pressure during exercise indicates some impediment to pulmonary flow induced by elevated or fixed

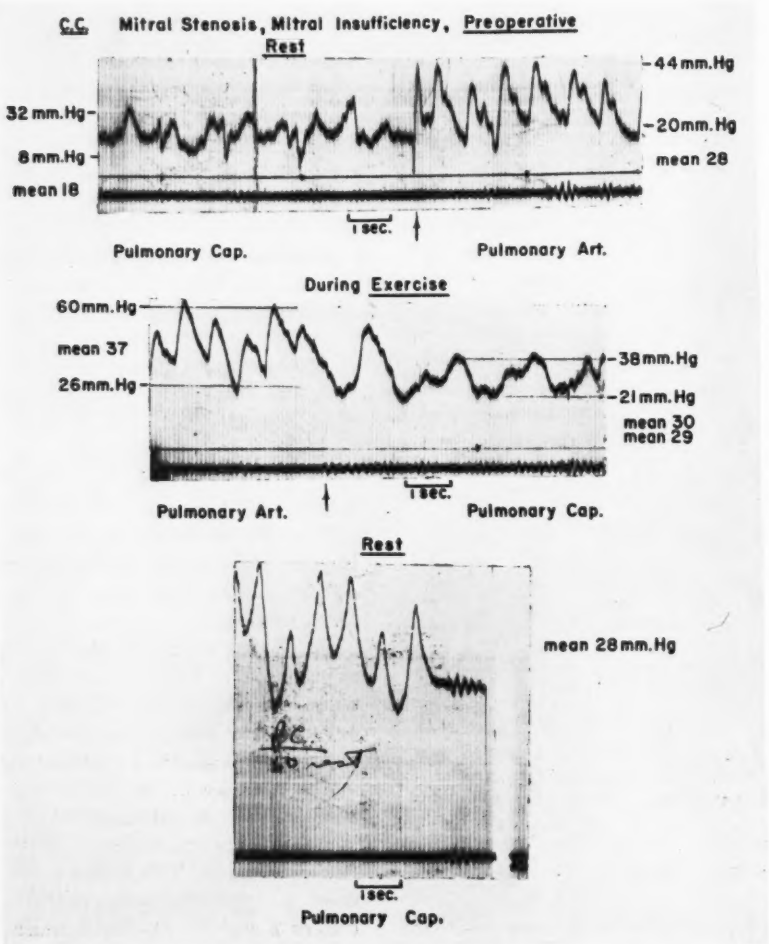


FIG. 4. Optical registration of pulmonary artery and pulmonary capillary pressure during rest and exercise. There is a rise in both pressures from rest to exercise. The high peaks of the pulmonary capillary pressure appears characteristic for mitral disease.

resistance in the pulmonary vascular bed or at the mitral valve. This problem will be discussed in a subsequent paragraph.

The pulmonary capillary pressure was elevated in all patients with mitral stenosis or insufficiency in whom it was recorded (tables 4 and 5). This indicates an elevation of the left auricular and pulmonary vein pressures.[12, 25] It is probable that this is primarily the result of the valvular disease. Cardiac failure may also be a contributory factor in the elevation of pulmonary capillary pressures. The correlation of the clinical history of pulmonary edema with the elevation in the pulmonary capillary pressure is interesting. In the 10 patients with mitral stenosis who gave a history of attacks of acute pulmonary edema, the pulmonary capillary pressure averaged 36.3 mm. Hg at rest and 43.5 mm. Hg on exercise. In patients with mitral stenosis without a history of pulmonary edema the average pulmonary capillary pressure was lower, averaging 23.1 mm. Hg at rest and 27.5 mm. Hg on exercise. In patients with mitral insufficiency, the pulmonary capillary pressures were lower than in patients with mitral stenosis (tables 4 and 5). Only 1 of these patients gave a history of pulmonary edema.

The results indicate that physiologic methods alone do not permit a clear differentiation between mitral stenosis and mitral insufficiency. There are certain features, however, which are more characteristic of one group than of the other. The resting cardiac output is lower and the resting arteriovenous oxygen difference greater in patients with predominant mitral insufficiency (tables 2 and 3). Exercise causes an average fall in cardiac output of 2.9 per cent in patients with mitral insufficiency (table 3). In patients with mitral stenosis, exercise results in an average increase of 9 per cent in the minute volume of circulation (table 2). It is conceivable that in mitral insufficiency regurgitation during systole is at least partially responsible for the fall in cardiac output. In patients with mitral insufficiency the oxygen consumption rises less during exercise and the increase in arteriovenous oxygen difference is more pronounced (figs. 1 and 2).

Fourteen of the patients of this series had clinical signs of peripheral congestive failure. It is therefore possible that some of the physiologic manifestations result from myocardial failure as well as from mitral disease. Decreased cardiac output, increased arteriovenous oxygen difference and elevated pulmonary artery and capillary pressures at rest can be manifestations of either mitral disease or myocardial failure.[21, 22] The disproportionate rise in pulmonary artery pressure with exercise as compared to the relatively small increase in cardiac output described above has also been observed in myocardial failure alone. However, an elevation of the right auricular pressure is usually evidence of right-sided failure. Thus, in all patients with mitral disease in whom the right auricular pressure was elevated, clinical signs of right-sided failure were apparent.

Results to be described in a subsequent report demonstrate that the residual volume of blood in the right ventricle is increased to from two to six times its normal value in patients with a history of myocardial failure and mitral disease.[27] Similar large volumes were found in patients with right-sided failure alone.[27] It is not surprising, therefore, that the physiologic manifestations of myocardial failure and mitral disease show such a close similarity.

Table 4 illustrates that the calculated pulmonary vascular resistance in mitral stenosis ranged from .62 to 20.8 mm. Hg per liter per minute per square meter of body surface, with an average of 6.19. In 5 patients with mitral insufficiency in whom pulmonary capillary pressures could be obtained, the pulmonary vascular resistance ranged from 4.7 to 22.5 mm. Hg./L./min./M.^{2}, with an average of 10.5 (table 5). These values are considerably higher than those found in normal individuals but not as high as those reported in pulmonary hypertension accompanying congenital heart disease.[7, 12]

The elevation of pulmonary vascular resistance found in the patients of this series suggests the presence of changes in the pulmonary vascular bed. The findings of Weiss

and Parker and of Larrabee and his co-workers furnish the anatomic basis for this increased pulmonary vascular resistance.[4, 28] Weiss and Parker described thickening of the pulmonary arterioles mainly due to intimal changes.[4] Necrotizing arteriolitis was also observed. Additional findings included elongation and dilatation of pulmonary capillaries and thickening of the capillary basement membrane. These findings were confirmed by Larrabee and Parker who found additional changes in the media of pulmonary arterioles.[18] They were of the opinion that vascular changes affecting the media might be reversed through operation at the mitral valve while the intimal changes are irreversible.

The question of reversibility of the vascular pathology in mitral stenosis is of importance. Surgical relief of the obstruction at the mitral valve decreases left auricular and pulmonary vein pressure.[29] Thus, it lessens the danger of pulmonary edema. But if the anatomic changes in the pulmonary vascular bed are irreversible, the operation would have no effect on pulmonary artery and right ventricular systolic pressures. Therefore, the pressure energy of the right ventricle would remain unchanged. As a result the possibility of right-sided heart failure would persist.

Physiologic studies offer some clue in this direction. If the pulmonary vascular changes in the lung are not fixed, then an increase in pulmonary blood flow should lead to decrease in the pulmonary vascular resistance, and operations eliminating the obstruction at the mitral valve should have the same effect.

Table 4 illustrates that the pulmonary vascular resistance fell in 2 and rose in 5 patients with mitral stenosis during exercise. In patients with mitral insufficiency vascular resistance fell in 2 and rose in an equal number (table 5). These findings indicate that there may be variations in the response of the pulmonary vascular bed of patients with mitral disease and that in a few the pulmonary vascular bed has not lost its normal ability to respond to an increased cardiac output by a fall in vascular resistance.

Results obtained in 4 patients after operation at the mitral valve further substantiate these findings. Although the effect of valvulotomy on the hemodynamics of patients with mitral disease will be the subject of a subsequent paper, the effect of the operation on pulmonary vascular resistance will be briefly discussed at this point. It may be seen from table 6 that following valvulotomy the pulmonary vascular resistance falls in every instance. This fall is primarily the result of a decline in pulmonary artery pressure. As the pulmonary artery pressure falls, so does the work of the right right ventricle (table 6). These findings suggest that the anatomic changes in the pulmonary vascular bed existing in patients with mitral disease may be reversible through operation.

TABLE 6.—*The Results of Mitral Valvulotomy on Pulmonary Pressures, Pulmonary Vascular Resistance and Pressure Energy of Right Ventricle*

Name		Date	Cardiac Output M.²	Mean Pulmonary Capillary Pressure mm. Hg	Mean Pulmonary Artery Pressure mm. Hg	Pulmonary Artery Resistance mm. Hg/L./min./M.²	Pressure Energy of R. V. Kg./M./min.
J. C.	Preop.	7/6/48	1.92		66	16*	1.72
	Postop.	1/19/50	2.43	22	31	3.7	1.02
D. E.	Preop.	11/7/49	2.17		60	11.4*	1.77
	Postop.	1/26/50	2.32	13	27	6.0	.85
F. C.	Preop.	1/5/50	1.49	32	63	20.8	1.28
	Postop.	4/3/50	1.72	29	41	6.9	.96

* Minimal resistance.

SUMMARY

Twenty-nine patients with mitral valvular disease have been studied by means of cardiac catheterization. Cardiac outputs, intracardiac, pulmonary arterial, and pulmonary capillary

pressures were determined during rest and exercise.

The resting cardiac output was reduced in all patients with mitral disease; exercise resulted either in a fall or a small increase in the minute volume of circulation. Increased arteriovenous oxygen difference was primarily responsible for the low cardiac outputs found during rest and exercise. The ratio of oxygen consumed per liter of ventilation fell during exercise.

Pulmonary artery and capillary pressures were elevated at rest and rose further with exercise; pulmonary capillary pressures were particularly high in patients with a history of pulmonary edema.

Physiologic methods did not permit a clear differentiation between mitral stenosis and mitral insufficiency. However, in general, in patients with mitral insufficiency, the resting cardiac output was lower, the arteriovenous oxygen difference was higher and exercise caused a greater fall in cardiac output.

The physiologic manifestations of mitral disease were compared with those resulting from myocardial failure. Large residual right ventricular blood volumes were found in congestive failure and in mitral disease with failure. However, the right auricular pressure and right ventricular residual volume were normal in mitral disease without failure. In the presence of failure the right auricular pressure was usually elevated.

The pulmonary vascular resistance in mitral disease was elevated. In some patients, exercise resulted in a decrease in the pulmonary vascular resistance. Valvulotomy reduced pulmonary vascular resistance in every case. The relationship of these findings to the anatomic changes in the pulmonary vascular bed were discussed.

REFERENCES

[1] Baker, C., Brock, R. C., and Campbell, M.: Valvulotomy for mitral stenosis. Brit. M. J. **1:** 1283, 1950.

[2] Bailey, C. P.: The surgical treatment of mitral stenosis (mitral commissurotomy). Dis. of Chest **15:** 377, 1949.

[3] Blalock, A.: Personal communication.

[4] Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path. **12:** 573, 1936.

[5] Schwedel, J. B.: Clinical Roentgenology of the Heart. New York, Paul B. Hoeber, 1946.

[6] Fishberg, A. M.: Heart Failure. Philadelphia, Lea and Febiger, 1940.

[7] Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B., Goodale, W. T., and Hellems, H. K.: Studies of the pulmonary circulation in man at rest. Normal variations and the interrelations between increased pulmonary blood flow, elevated pulmonary arterial pressure and high pulmonary "capillary" pressure. J. Clin. Investigation **29:** 602, 1950.

[8] Borden, C. W., Ebert, R. V., Wilson, R. J., and Wells, H. S.: Pulmonary hypertension in heart disease. New England J. Med. **242:** 529, 1950.

[9] Bloomfield, R. A., Tareson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. J. Clin. Investigation **25:** 639, 1946.

[10] Lenègre, J., and Maurice, P.: Average right ventricular pressure in man; the normal and in heart disease. Stanford M. Bull. **5:** 61, 1947.

[11] Nomenclature and Criteria for Diagnosis of Diseases of the Heart. New York, New York Heart Association, 1939.

[12] Calazel, P., Gerard, R., Daley, R., Draper, A., Foster, J., and Bing, R. J.: The comparison of the right and left auricular, capillary and pulmonary artery pressures in nine patients with auricular septal defect. Bull. Johns Hopkins Hosp. **88:** 20, 1951.

[13] Van Slyke, D. D., and Neill, J. M.: Determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. **61:** 523, 1924.

[14] Fick, A.: Über die Messung des Blutquantums in den Herzventrikeln. Sitzung. phys. med. Gesell. zu Wurzburg. Jul. 1870. P. 16.

[15] Bing, R. J., Heimbecker, R. O., Falholt, W., Carroll, D., and Friedlich, A.: A method for the approximation of residual volume in the right ventricle of man. Am. J. Physiol. **163:** 698, 1950.

[16] Bing, R. J., Friedlich, A., and Blount, S. G.: Physiological studies in congenital heart disease. IX. Circulatory dynamics of the anomalies of venous return to the heart including pulmonary arteriovenous fistula. Bull. Johns Hopkins Hosp. **86:** 20, 1950.

[17] C. L. Evans, ed.: Starling's Principles of Human Physiology, ed. 7. Philadelphia, Lea and Febiger, 1936.

[18] Prec, O., Katz, L. N., Sennett, L., Rosemann, R. H., Fishman, A. P., and Hwang, W.: Deter-

mination of kinetic energy of the heart in man. Am. J. Physiol. **159:** 483–491, 1949.

[19] BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR.: Physiological studies in congenital heart disease. III. Results obtained in five cases of Eisenmenger's complex. Bull. Johns Hopkins Hosp. **80:** 323, 1947.

[20] COURNAND, A.: Recent observations in the dynamics of the pulmonary circulation. Bull. New York Acad. Med. **23:** 27, 1947.

[21] HICKAM, J. B., AND CARGILL, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation **27:** 10, 1948.

[22] STEAD, E. A., JR., WARREN, J. V., AND BRANNON, E. S.: Cardiac output in congestive heart failure. Am. Heart J. **35:** 529, 1948.

[23] COURNAND, A., AND RICHARDS, D. W., JR.: Pulmonary insufficiency. Am. Rev. Tuberc. **44:** 26, 1941.

[24] BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR.: Physiological studies in congenital heart disease. II. Results of operative studies with tetralogy of Fallot. Bull. Johns Hopkins Hosp. **80:** 121, 1947.

[25] HELLAMS, H. K., HAYNES, F. W., DEXTER, L., AND KINNEY, T. D.: Pulmonary capillary pressure in animals estimated by venous catheterization. Am. J. Physiol. **155:** 98, 1948.

[26] LAGERLÖF, H., AND WERKO, L.: Studies in the circulation of blood in man. VI. The pulmonary capillary venous pressure pulse in man. Scandinav. J. Clin. & Lab. Investigation, **1:** 147, 1949.

[27] BING, R. J., FALHOLT, W., CARROLL, D., HEIMBECKER, R. O., WELLS, R. E., MUDD, G., AND FERENCZ, C.: The measurement of the residual volume in the right ventricle of normal individuals and of patients in cardiac failure and mitral disease. To be published.

[28] LARRABEE, W. F., PARKER, R. F., AND EDWARDS, J. F.: Pathology of intrapulmonary arteries and arterioles in mitral stenosis. Proc. Staff. Meet. Mayo Clin. **24:** 316, 1949.

Circulatory and Respiratory Effects of Adenosine Triphosphate in Man

By Dean F. Davies, M.D., Arthur L. Gropper, M.D., and Henry A. Schroeder, M.D.

The authors have studied the acute effects of the intravenous and intra-arterial injection of the sodium salt of adenosine triphosphate (ATP) in man. Rapid injection causes a frightening sensation in the chest and hyperpnea. The changes found agree with those reported in cats and are consistent with the concept that adenosine triphosphate is a vasodilator in somatic structures but causes an increase in pulmonary vascular and possibly in splanchnic resistance. Its principal action seems to be pharmacologic rather than in its role as an intracellular metabolite.

ALTHOUGH the important role of adenosine triphosphate (ATP) as a coenzyme in transfer of high-energy phosphate is widely recognized,[1] there is no available information on its pharmacologic effects in man. Increasing attention has been directed toward adenosine compounds since the demonstration by Drury and Szent-Györgyi[2] that adenosine and adenylic acid dilate the coronary vessels and lower arterial blood pressure in cats and dogs. They suggested that this activity was associated with the ease of deamination of the compounds. Fleish and Domenjoz[3] compared the effects of muscle adenylic acid with adenosine triphosphate on blood flow in the hind limb of dogs and concluded that adenosine triphosphate was 70 times as effective as an equimolar concentration of muscle adenylic acid in its vasodilatory action. Kalckar and Lowry[4] did not find that the presence of its two pyrophosphate groups made adenosine triphosphate any more potent in its vasodepressor effect on rabbits than muscle adenylic acid.

On the basis of its vasodilator effect several suggestions have been made that one of these compounds may be responsible for the vasodilatation occurring in states of shock.[5-9] Potter[10] suggested that the phosphorylating mechanism may be lost, a concept which could link shock with the high phosphate-bond energy of adenosine triphosphate rather than with its ease of deamination. By injecting a mixture of adenyl pyrophosphatase, alkaline phosphatase, and adenosine deaminase intravenously in rabbits receiving an infusion of adenosine triphosphate, Kalckar and Lowry[4] were able to block the depressor effect of adenosine triphosphate. However, when these enzymes were injected into rabbits and dogs in traumatic shock, no protective action on blood pressure occurred and insignificant amounts of adenosine derivatives were found in the blood. They concluded that the release of adenylic acid compounds probably does not play a primary role in the etiology of traumatic shock.

It first seemed reasonable to Szent-Györgyi[11] that the energy for the breakdown of adenosine triphosphate is necessary for the relaxation of muscle to a state of high potential energy. Ruskin[12] claims this confirms what he "had already proved through the clinical use of the adenylic nucleotide." Clinical experience led him to believe that adenosine triphosphate does not seem to influence hypertension, while the iron salt of yeast adenylic acid (Ironyl) is clinically effective in hypertension, circulatory failure,[13] muscle spasm and arthritic pain.[12, 14] One of us (H.A.S.)[15] found no reduction in blood pressure from Ironyl in a hypertensive patient. However he observed a delayed, prolonged fall in blood pressure after adenosine triphosphate in 2 patients with malignant hypertension. One became increasingly resistant to daily intravenous injections of the drug over a period of two months. One patient with chronic glomerulonephritis and 1 with early

From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine, and St. Louis City Hospital, St. Louis, Missouri.

Supported by a grant-in-aid from the National Heart Institute, United States Public Health Service.

malignant hypertension showed no response which could exclusively be attributed to adenosine triphosphate.

In spite of the claims of Ruskin and others[16, 17] of the clinical effectiveness of adenosine triphosphate and adenosine derivatives in vasospastic diseases, there is growing evidence that the action of these compounds is not primarily due to their role in muscle metabolism. Vasoconstriction results from adenosine triphosphate[18, 19] and adenosine[5] in the pulmonary vessels and from adenosine[2, 20] in the kidney; prompt dilatation results from adenosine and adenylic acid in coronary and ear vessels in the absence of high-energy phosphate.[5] These facts have not been explained. A study of the acute effects of adenosine triphosphate on the respiratory and hemodynamic physiology of man was therefore considered worthwhile in order to study its pharmacologic action and because of claims of its therapeutic possibilities.

Methods

Subjects. Twenty-eight white patients were studied; they were selected from the St. Louis City Hospital Divisions and Out-Patient Departments and ranged in age from 16 to 79 years. The group included 11 hypertensive and 17 normotensive patients convalescent from arthritis, acute alcoholism, pneumonia, peptic ulcer and a number of other conditions. Six were women, the remainder men. Each patient was studied for a 30 to 80 minute period in a quiet laboratory maintained at 22 to 25.5 C. during the experiment.

Three major approaches were made to the problem: (1) adenosine triphosphate was given intravenously to 19 subjects while estimates of changes in respiration, cardiac output, blood pressure, and digital blood flow were carried out; (2) intra-arterial injection was made into 4 lightly anesthetized and 6 unanesthetized patients while measurements of relative changes in blood volume in ipsi- and contralateral fingers were made; (3) adenosine triphosphate was given intravenously to 1 lightly anesthetized and 7 unanesthetized patients during renal clearance studies. Results of digital blood flow, cardiac output and blood pressure measurements made in several of these patients are discussed under the first approach. Satisfactory measurements of all parameters under each approach were obtained with a few exceptions.

Respiration. A pneumograph with rubber diaphragm and an air conducting system was used.

Cardiac Output. Tracings were taken on a high frequency ballistocardiograph of Wilkins' design.[23] Oscillations of the table were recorded by means of a photoelectric pressure recorder using a rubber membrane of suitable natural frequency of vibration. The calculations were made from representative strips of the record, by applying the area formula of Starr.[24]

Blood Pressure. Direct brachial arterial blood pressure was measured by the use of a Hamilton optical manometer in some instances; an aneroid sphygmomanometer was used in others.

Blood Flow. Qualitative changes in blood flow were estimated by photoelectric plethysmographs applied to the ear and finger.

Venous Pressure. A water manometer containing 2.5 per cent sodium citrate measured antecubital venous pressure directly.

All electrical signals were led through direct-coupled amplifiers into Sanborn Galvanometers and recordings made optically on a photokymograph run at a speed of 5 or 25 mm. per second.

Renal Function. Two control urine collection periods of 10 to 12 minutes each were taken according to the constant infusion routine.[25] In the patient who received sodium amytal only 300 cc. of water was given by mouth. Priming and sustaining infusion solutions were prepared with inulin and sodium paraaminohippurate (PAH) according to formulas based on weight, estimated renal function and age.[26] Analysis for inulin was made by Harrison's method,[27] modified for the Beckman DU Spectrophotometer. Analyses for paraaminohippurate were made by the method of Smith[28] except that 1:15 acid zinc sulfate filtrates were used instead of cadmium sulfate and sodium hydroxide.

After careful reassurance during the time instruments were being applied, two or three control clearance periods and one or more control tracings were taken. Forty or more mg. of adenosine triphosphate* freshly dissolved in 50 cc. of sterile saline was infused at a rate of approximately 5 cc. per minute depending somewhat on the subjective reactions of the patient; continuous measurements were taken during the injection interval. In most instances the total dose was 40 mg., the range being 20 to 75 mg. Records were taken at varying intervals during recovery.

Results

The subjective responses to intravenous injection of adenosine triphosphate were striking. Patients invariably experienced a sensation in

* Sodium salt of adenosine triphosphate obtained from Rohm and Haas Company. Assay by the hexokinase reaction performed by Dr. David Brown on different batches of adenosine triphosphate from the same company yielded 67 to 72 per cent active substrate. The compound was kept desiccated in the refrigerator or in deep freeze.

their chest which they found difficult to describe. Some felt it was easier to breathe, while others felt suffocated. A few became very apprehensive, especially if they were not fully prepared for the effects. About half of them coughed if the injection was rapid. The subjective effects were always more marked than any of the objective changes noted, but they disappeared almost immediately when the injection was stopped.

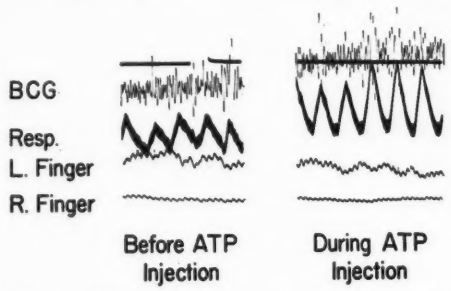


FIG. 1. Effect of intravenously administered adenosine triphosphate on respiratory volume. Ballistocardiogram (B.C.G.), right (R) and left (L) finger plethysmograms are also shown. Patient C. S. ♂. Photokymograph speed 5 mm. per second.

On intra-arterial injection the subjective response was greatly lessened for an equal dose but was present if injection was sufficiently rapid. After injection in the brachial artery the chief sensations were warmth throughout the forearm and hand; the skin of the injected forearm was distinctly warmer to touch than that of the opposite side, and some patients experienced a feeling of fullness in it.

TABLE 1.—*Effect of Adenosine Triphosphate on the Heart*

Case	Patient	Age	ATP Dose	Cardiac Index			Pulse Rate		
				Av. Control	Max. Exptl.	1st Recov.	Av. Control	Max. Exptl.	1st Recov.
Intravenous									
		Yrs.	*Mg.*	*L./min./sq.m.*	*L./min./sq.m.*	*L./min./sq.m.*	*beats/min.*	*beats/min.*	*beats/min.*
1	F. M. ♂	49	40	*3.31*	—	*3.45*	*112*	*116*	*116*
2	B. M. ♂	24	40	2.34	2.95	*2.42*	61	75	*66*
3	L. M. ♂	22	40	2.78	2.79	*2.42*	64	72	*75*
4	D. D. ♂	33	40	3.96	3.78	*3.81*	85	86	*90*
5	T. B. ♂	47	40	3.25	3.76	*4.21*	84	87	*98*
6	T. C. ♂	37	40	3.39	3.54	—	78	102	—
7	A. L. ♂	60	40	4.16	4.76	*4.71*	88	88	*102* Amytal sed.
8	P. W. ♂	36	32	2.90	2.70	*2.51*	86	80	*76*
9	C. F. ♂	52	35	2.20	2.06	*2.29*	62	64	*76*
10	F. T. ♂	67	75	2.68	2.97	*2.59*	80	92	*80*
11	L. F. ♀	24	8	2.83	3.69	*5.90*	97	140	*140*
12	A. S. ♂	30	40	3.20	3.25	*3.64*	90	110	*104*
Mean				3.06	3.30		80	90	
Intra-arterial									
1	J. W. ♂	73	40	2.61	2.62	—	70	70	—
2	J. McC. ♂	56	40	2.51	3.79	*3.68*	92	96	*96*
3	F. P. ♀	24	40	2.32	2.18	—	88	80	—
4	H. S. ♂	72	40	2.64	5.15	*3.92*	84	93	*91*
5	A. H. ♀	26	25	2.40	3.26	*3.41*	92	126	*128* Amytal sed.
6	H. L. ♂	53	40	3.46	4.08	*3.69*	89	100	*98* Amytal sed.
7	E. V. ♂	16	40	2.88	3.12	*3.32*	93	118	*110* Amytal sed.
8	C. S. ♂	50	40	3.08	5.35	*3.78*	100	117	*99*
Mean				2.74	3.69		88	100	

Figures in italics were not used in estimating means in order to keep the data comparable.
"First recovery" values represent measurements made from 1 to 10 minutes after drug injection stopped.

Respiration. The most profound and consistent changes were observed in the depth of respiration. Although no quantitative measurement of respiratory volume was attempted, markably constant in all but 2 subjects. One increased from 12 to 32 respirations per minute during intravenous injection, the other from 18 to 32 during intra-arterial injection.

TABLE 2.—*Blood Pressure Effects of Adenosine Triphosphate*

Case No.	Patient	Age	ATP† Dose	Method*	Control		During Injection		Recovery		Post Injection	Remarks
					Sys.	Dias.	Sys.	Dias.	Sys.	Dias.		
Intravenous												
		Yrs.	*Mg.*		*mm. Hg.*		*mm. Hg.*		*mm. Hg.*		*Min.*	
1	T. P. ♂	62	40	C	*230*	*138*	—	—	*250*	*130*	1	Hypertensive
2	P. W. ♂	36	32	H	*195*	*87*	—	*88*	*189*	*88*	20	Hypertensive
3	P. K. ♀	62	20	C	*230*	*114*	—	—	*260*	*120*	10	Hypertensive
4	F. T. ♂	67	75	H	228	90	203	78	*214*	*80*	2	Hypertensive
5	L. F. ♀	24	8	H	218	119	202	114	*195*	*114*	2	Hypertensive
6	P. W. ♂	36	20	H	160	85	162	74	*161*	*81*	4	Hypertensive
7	C. F. ♂	52	35	H	220	90	216	78	*230*	*92*	1	Hypertensive
8	A. S. ♂	30	40	H	190	105	206	110	*190*	*100*	10	Hypertensive
9	F. M. ♂	49	40	C	*118*	*68*	—	—	*118*	*72*	2	Normotensive
10	A. L. ♂	60	40	C	*130*	*74*	—	—	*128*	*68*	1	Normotensive, Amytal
11	T. C. ♂	37	40	C	*108*	*60*	—	—	*104*	*70*	5	Normotensive
12	A. G. ♂	35	34	C	84	58	83	54	*80*	*50*	3	Normotensive, Amytal
13	D. D. ♂	33	40	C	98	75	94	70	*94*	*68*	2	Normotensive
14	T. B. ♂	47	40	H	137	62	134	50	*111*	*54*	1	Normotensive
15	L. M. ♂	22	40	C	*108*	*62*	—	—	*120*	*70*	6	Normotensive
16	B. M. ♂	24	40	H	112	60	96	47	*106*	*44*	1	Normotensive
17	P. P. ♂	53	40	C	*180*	*90*	—	—	*168*	*90*	11	Normotensive
Mean					160.8	82.7	155.2	75.0				
Intra-arterial												
1	C. S. ♂	50	40	C	130	75	—	—	150	94	7	Normotensive
2	W. H. ♂	79	40	C	135	70	—	—	135	60	9	Normotensive
3	L. P. ♂	45	40	C	128	70	—	—	132	80	33	Normotensive
4	J. W. ♂	73	40	C	130	75	—	—	150	94	7	Normotensive
5	J. McC. ♂	56	40	C	112	70	—	—	118	68	12	Normotensive
6	H. S. ♂	72	40	C	138	78	—	—	150	82	18	Normotensive
7	A. H. ♀	26	25	C	108	72	*116*	*90*	118	82	3.5	Normotensive
8	E. V. ♂	16	40	C	140	64	*130*	*66*	148	68	1	Normotensive
9	H. L. ♂	53	40	C	127	77	*150*	*88*	138	76	1	Normotensive
Mean					127.6	72.3			137.7	78.2		

† Expressed as adenosine triphosphate, given as sodium salt.

* C—cuff, H—Hamilton.

Figures in italics were not used in estimating means in order to keep the data comparable. "First recovery" values represent measurements made at varying intervals after injection was stopped as indicated in column labeled "Post Injection".

an approximation of this parameter was made from measurements of the pneumograph tracings (fig. 1). This indicated an average increase of 70 per cent during intravenous injection and a somewhat smaller increase during intra-arterial injection. Respiratory rate remained re-

Cardiac Effects. The effects of intravenous and intra-arterial injections on the heart are shown in table 1. No consistent effects on cardiac index were noted. On intravenous injection, the maximum change in cardiac index from its control value averaged +0.24 L. per

minute per square meter of body surface, although there was either no significant change or a slight fall in 5 of 11 cases. On intra-arterial injection the cardiac index averaged 0.95 L. per minute per square meter higher than the controls, although in 2 of 8 cases there was no essential change. All 3 of the subjects under Amytal sedation showed increases of more than 10 per cent. Statistical analysis of the changes produced by the intravenous injection gave a t value of 2.25, below the level of significance.

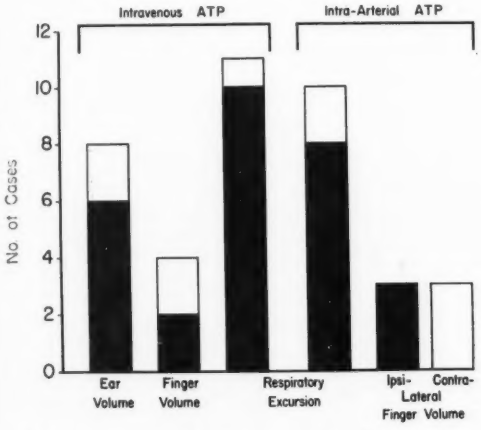


FIG. 2. Effect of intravenous adenosine triphosphate (ATP) on ear volume, finger volume and respiratory stroke volume, and effect of intra-arterial ATP on respiratory stroke volume, ipsi- and contralateral finger volume. Number of cases showing increase in each function is represented by solid portion, no increase by open portion of bars.

The increase in cardiac index was associated with an increase in pulse rate in every instance. An increase of 8 or more beats per minute occurred in 8 of 15 subjects on intravenous injection, the average being 10 beats per minute. Heart rate fell in one subject.

The observed rises in cardiac output were not accounted for on the basis of pulse rate alone in 4 subjects whose stroke index increased significantly.

Arterial and Venous Pressure; Volume Flow. It will be noted in table 2 that during intravenous injection both systolic and diastolic blood pressure showed small decreases in 7 of 9 subjects, the diastolic change being statistically significant, and averaging 7 mm. Hg. Observations of blood pressure during intra-arterial injection were incomplete, but measurements taken at varying intervals during recovery showed a return to control systolic values or above in every instance. In only one (W.H.) was the first diastolic pressure significantly below its control level after recovery.

Venous pressure showed small increases in 3 of 4 subjects during intra-arterial injections and in the only subject where this measurement was made during intravenous injection.

TABLE 3.—*Acute Effects of Adenosine Triphosphate on Renal Function of Man*

Patient	Age	Wt.	No. of Control Periods	Inulin Clearance			PAH Clearance			Filtration Fraction		
				Mean Control	Change During ATP Injection	Change After‡ ATP Injection	Mean Control	Change During ATP Injection	Change After‡ ATP Injection	Mean Control	Change During ATP Injection	Change After‡ ATP Injection
	yrs.	*lbs.*		*cc./min.*	*per cent*		*cc./min.*	*per cent*		× *100*	*per cent*	
P. K. ♀	65	111	2	47.9	−9.4	−1.0	172	−10.1	−10.8	27.9	+0.4	+11.5
P. W. ♂	36	155	2	120.0	+0.7	−1.9	364	−9.5	−3.7	33.0	+11.2	+5.6
C. F. ♂	49	199	2	80.6	−8.1	−15.1	245	−18.4	−11.6	32.8	+12.5	−3.7
T. P. ♂	62	156	3	67.9	−18.4	−5.8	266	−1.1	−0.7	25.5	−19.2	−12.5
M. L. ♂	22	190	2	148.2	−11.7	+7.6	671	−25.9	−12.9	22.2	+18.5	+21.4
M. G. ♂*	47		3	120.7	−39.1	—	493	−37.3	—	26.7	−10.5	—
F. T. ♂	55	150	3	111.3	−15.4	+7.1	339	−18.3	+19.2	33.0	+2.7	−10.6
A. L. ♂*, †	59	131	2	65.6	−24.4	+13.7	299	−25.0	−15.0	21.9	+0.9	+11.3
Mean				95.3	−15.7		356	−17.9		27.9	+4.9	

* Normotensive patients. Remainder were hypertensive.

† Patient received a three-quarter dose of Sodium Amytal intravenously 20 minutes before beginning control clearance periods.

‡ Recovery periods followed injection periods.

Photoelectric plethysmography in 3 subjects during injection into a brachial artery gave definitive evidence of increased finger volume in the ipsilateral but not contralateral side (fig. 2). During intravenous injection changes in ear and finger were less clear-cut. Six of 8 subjects showed evidence of increased blood volume in ear and 2 of 4 increased blood volume in finger.

Renal Function. Table 3 shows the effects of intravenous injection of adenosine triphosphate on glomerular filtration rate, effective renal plasma flow, and filtration fraction on 7 unanesthetized patients and 1 patient who had received 0.5 Gm. of Sodium Amytal intravenously before the control periods. With one exception, there was a fall in paraaminohippurate clearance during the injection with a tendency to return to normal during the recovery period. Inulin clearance decreased during injection in 7 out of 8 subjects. Two patients who were apprehensive showed evidence of efferent arteriolar constriction by an elevated filtration fraction. Although this response would be expected after the administration of adenosine triphosphate, the net effect on filtration fraction during recovery was negligible.

Discussion

The many compensatory and defense mechanisms of an intact circulation tend to increase the number of possible interpretations of the results in a study such as the present one. When results are not consistent, they are more likely to be produced by such secondary mechanisms, and not reflect direct responses to the injection of a drug. According to this reasoning, the present data on changes of respiratory rate, renal blood flow, heart rate, and cardiac output may not represent direct responses to the action of adenosine triphosphate. The observations on patients under Amytal sedation suggest this measure was not successful in eliminating the secondary mechanisms. On the other hand, the moderate but more consistent changes in blood pressure, digital volume flow and venous pressure may well be a direct result of adenosine triphosphate, suggesting a vasodilatory action. There is ample documentation in other studies[2–5] for such an effect. The lack of consistency in the response of the above functions suggest that they are not controlled by the direct action of adenosine triphosphate on muscle contraction. Indeed, Sandow[21] has questioned the original theory of Szent-Györgyi on the role of adenosine triphosphate in muscle relaxation, and Szent-Györgyi himself has recently[22] modified his views.

The one striking and consistent response was hyperpnea, which occurred even in subjects under moderate Amytal sedation who could not have been apprehensive. Of the chemical factors concerned with the regulation of respiratory rate and depth, hydrogen ion concentration, carbon dioxide tension and oxygen tension are known to be important. Adenosine triphosphate may prove to influence this chemical regulation through the central nervous system. On the other hand, the response could be secondary to local factors such as increased pulmonary artery resistance.

No significant difference was observed in the response of hypertensive and normotensive subjects. The decrease in renal function obtained in these acute experiments provide an argument against the therapeutic usefulness of adenosine triphosphate. Suggestive evidence that a delayed beneficial effect is not invariable was provided by the follow-up clearance on one patient (C.F.). Effective renal plasma flow and blood pressure carried out the morning after adenosine triphosphate administration in this case had returned to control levels.

Although the interpretation of these results cannot be definitively stated, they are on the whole in accord with published data on the effects of adenosine triphosphate in animals, particularly those of Emmelin and Feldberg.[14] Comparison of their findings in chloralosed cats and our results in man is made in table 4. The results of the two approaches agree remarkably well. They are compatible with the concept that adenosine triphosphate is a vasodilator in somatic structures, causes a marked increase in pulmonary vascular resistance, and through chemical or reflex pathways produces an involuntary increase in respiratory volume. The evidence is suggestive that splanchnic blood flow decreases. Some of the variable effects seen in blood pressures, heart rates, and

cardiac outputs may be attributed to the dependence of the response on the concentration of adenosine triphosphate as found by Gropp[29] and Bugachev[30] in perfusion studies on frogs. However, if neurogenic mechanisms are not blocked by adenosine triphosphate, they may exert varying degrees of compensatory response. Either alternative would offer strong support to the concept that injected adenosine triphosphate acts pharmacologically rather than metabolically and does not have its effect directly on the contractile system of the smooth muscle of the vascular wall.

TABLE 4.—*Effect of Adenosine Triphosphate on Respiratory and Cardiovascular Physiology*

	Emmelin and Feldberg[14]	Present Study
	Chloralosed Cats	*Man*
Blood pressure	Profound fall	Moderate fall
Respiratory Volume	Marked increase	Marked increase
Respiratory Rate	Variable	No change
Heart Rate	Slowed*	Not consistent
Cardiac Output	Decreased†	Not consistent
Venous Pressure	Elevated	Elevated
Renal Blood Flow	—	Decreased
Peripheral Vessels	Dilatation‡	Dilatation

* Interpreted as result of vagus reflex.

† Inferred from "strong obstruction in pulmonary circulation."

‡ By inference from effect on blood pressure.

SUMMARY

1. Adenosine triphosphate (ATP) was injected intravenously and intra-arterially into hypertensive and normotensive patients while various respiratory and cardiovascular functions were measured.

2. Subjective response was striking and consisted of a peculiar, painless sensation in the chest and apprehension.

3. Depth of respiration increased markedly without change of respiratory rate.

4. Cardiac output remained constant or rose.

5. Blood pressures, especially diastolic, showed a moderate fall.

6. On intra-arterial injection vasodilatation occurred in the injected extremity. On intravenous injection peripheral dilatation usually took place where measured (finger and ear).

7. A rise in venous pressure occurred in 3 of 4 subjects during injection.

8. Effective renal plasma flow and glomerular filtration rate usually decreased.

9. The compatibility of these results with known effects of adenosine triphosphate in animals is pointed out.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation for the cooperation of Dr. Joseph E. Weldon and the house staff of City Hospital in selection of several of the patients used. The technical assistance of Miss Willa Brunkhorst, Mrs. Gay Goldstein, and Miss Betty Wheeler is gratefully acknowledged.

REFERENCES

1 LIPMANN, F., AND KAPLAN, N. O.: Intermediary metabolism of phosphorus compounds. Ann. Rev. Biochem. **18:** 267, 1949.

2 DRURY, A. N., AND SZENT-GYÖRGYI, A.: The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J. Physiol. **68:** 213, 1929–30.

3 FLEISCH, A., AND DOMENJOZ, R.: The vasodilatory effect of adenine acid and adenosinetriphosphoric acid. Klin. Wchnschr. **19 (2):** 984, 1940.

4 KALCKAR, H. M., AND LOWRY, O. H.: The relationship between traumatic shock and the release of adenylic acid compounds. Am. J. Physiol. **149:** 240, 1947.

5 BENNET, D. W., AND DRURY, A. N.: Further observations relating to the physiological activity of adenine compounds. J. Physiol. **72:** 288, 1931.

6 GREEN, H. N.: Shock-producing factor(s) from striated muscle. I. Isolation and biological properties. Lancet **2:** 147, 1943.

7 BIELSCHOWSKY, M., AND GREEN, H. N.: Shock-producing factor(s) from striated muscle. II. Fractionation, chemical properties and effective doses. Lancet **2:** 153, 1943.

8 STONER, H. B., AND GREEN, H. N.: Adenosine compounds and phosphates in the blood of shocked rabbits. J. Path. and Bact. **56:** 343, 1944.

9 —, AND —: Further observations on the adenosine equivalent of the blood of rabbits following lethal forms of tissue injury. J. Path. and Bact. **57:** 337, 1945.

10 POTTER, V. R.: Coupling between phosphorylation and oxidation of the 4-carbon acids in rat kidney homogenates. Arch. Biochem. **6:** 439, 1945.

[11] SZENT-GYÖRGYI, A.: Chemistry of Muscular Contraction. New York, Academic Press, Inc., 1947.

[12] RUSKIN, S. L.: A newer concept of arthritis and the treatment of arthritic pain and deformity by sympathetic block at the sphenopalatine (nasal) ganglion and the use of the iron salt of the adenyl nucleotide. Am. J. Digest. Dis. **16:** 386, 1949.

[13] —: The dynamics of muscle tonus and its relationship to circulatory failure. Am. J. Digest. Dis. **15:** 261, 1948.

[14] —: The control of muscle spasm and arthritic pain through sympathetic block at the nasal ganglion and the use of the adenyl nucleotide. Contributions to the physiology of muscle metabolism. Part II. Am. J. Digest. Dis. **13:** 311, 1946.

[15] SCHROEDER, H. A.: Personal communication.

[16] SZENT-GYÖRGYI, A.: *Loc. cit.*, p. 78.

[17] HERBRAND, W.: Die biologische und pharmakotherapeutische Bedeutung der körpereigenen muskeladenosinephosphorsäure. Deutsche med. Wchnschr. **63:** 1841, 1937.

[18] EMMELIN, N., AND FELDBERG, W.: Systemic effects of adenosine triphosphate. Brit. J. Pharmacol. & Chemotherapy **3:** 273, 1948.

[19] GADDUM, J. H., AND HOLTZ, P.: The localization of the action of drugs on the pulmonary vessels of dogs and cats. J. Physiol. **77:** 139, 1933.

[20] MARCOU, I.: Sur l'action vasculaire élective de l'adénosine. Compt. rend. Soc. de biol. **109:** 985, 1932.

[21] SANDOW, A.: Muscle. Ann. Rev. Physiol. **11:** 297, 1949.

[22] SZENT-GYÖRGYI, A.: Attacks on muscle. Science **110:** 411, 1949.

[23] WILKINS, R. W.: A tilting ballistocardiograph. Am. Heart J. **26:** 351, 1943.

[24] STARR, I., AND SCHROEDER, H. A.: Ballistocardiogram. II. Normal standards, abnormalities commonly found in diseases of the heart and circulation, and their significance. J. Clin. Investigation **19:** 437, 1940.

[25] GOLDRING, W., AND CHASIS, H.: Hypertension and Hypertensive Disease. The Commonwealth Fund, New York, 1944.

[26] DAVIES, D. F., AND SHOCK, N. W.: Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J. Clin. Investigation **29:** 496, 1950.

[27] HARRISON, H. E.: A modification of the diphenylamine method of determination of inulin. Proc. Soc. Exper. Biol. & Med. **49:** 111, 1942.

[28] SMITH, H. W., FINKELSTEIN, N., ALIMINOSA, L., CRAWFORD, B., AND GRABER, M.: The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. Clin. Investigation **24:** 388, 1945.

[29] GROPP, W.: Die Wirkung von Adeninsulfat, Muskeladenylsäure und Adenosintriphosphorsäure im Froschdurchströmungs präparat und auf den Blutdruck des Kaninchens. Arch. f. exper. Path. u. Pharmakol. **199:** 216, 1942.

[30] BUGACHEV, A. G.: Effect of adenosine triphosphate on blood vessels. Byull. eksper. biol. e med. **23:** 35, 1947.

Production of Prolonged Arterial Hypertension in Dogs by Chronic Stimulation of the Nervous System

Exploration of the Mechanism of Hypertension Accompanying Increased Intracranial Pressure

By ROBERT D. TAYLOR, M.D., AND IRVINE H. PAGE, M.D.

We were unable to produce chronic arterial hypertension in dogs by severe cerebral ischemia induced by ligation of blood supply to the brain. Combining cerebral ischemia with the mechanical effect of a wire in the floor of the fourth ventricle and the thermal stimulus of heat generated in this wire by short wave diathermy resulted in hypertension that lasted as long as 10 months. Experiments are described which indicate that the arterial hypertension which accompanies increased cerebrospinal fluid pressure is in part the result of pressure on the brain and not entirely due to cerebral anemia.

IN 1947 we described a method for the production in dogs of arterial hypertension of neurogenic origin which lasted several hours.[1] It depended upon heating with short wave diathermy a wire embedded in the floor of the fourth ventricle. However, attempts to establish permanent hypertension by prolonged and repeated stimulation were not successful, apparently because glial tissue about the wire effectively insulated the pressor areas against heat generated within the wire.

The present study was undertaken because of the observation that 2 of the dogs with wire implanted in the medulla, subjected to progressive ligation of the arteries supplying the brain, developed arterial hypertension which lasted 8 to 10 months while otherwise normal dogs having similar operations to produce cerebral ischemia either had normal blood pressures or were hypertensive for two weeks or less. Several groups of experiments are reported which confirm the view that the combination of cerebral anemia and stimulation of pressor areas of the brain produce more marked and longer lasting hypertension than either one alone.

From the Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

METHODS

Experiments were carried out on 165 mongrel dogs. For surgical operations and treatment with diathermy the animals were anesthetized with pentobarbital, 35 mg. per Kg. of body weight given by intravenous injection. Operative procedures were carried out with sterile technic. Short-wave diathermy was applied to animals' heads with an ordinary clinical diathermy apparatus. The heads were wrapped with toweling so that three to four inches separated the coils of the apparatus from the skin. Blood pressures were measured with a mercury manometer after puncture of a femoral artery.

The blood vessels supplying the brain were ligated through a midline incision low in the neck. By means of blunt dissection, adequate retraction, and traction upon the carotid arteries, it was possible to deliver into view the origins of the carotid, vertebral, thyrocervical trunk, costocervical, and internal mammary arteries. Vessels were doubly ligated and a 0.5 to 1.0 cm. segment was resected from between the ligatures.

If only the vertebral and carotid arteries were to be served this was done at a one stage operation. If all the vessels were to be interrupted, all save a single carotid were cut during the first stage. The remaining carotid was ligated under local anesthesia three to six days later. Hereafter "ligation of vessels" refers to the two stage operation unless otherwise indicated. This technic gave a high mortality rate. However, less drastic measures were ineffective in producing even transient hypertension. If gradual occlusion of the remaining carotid was accomplished in stages by tightening a Goldblatt clamp on it, no elevation of pressure occurred.

For exposure of the floor of the fourth ventricle, dogs were placed in a prone position with the head in a holder which extended the neck from the body and flexed the head on the neck. A midline incision which extended downward from the occipital protuberance exposed the lower edge of the occipital bone. A 2 cm. square portion of the occipital bone was removed with a ronguer. Reflection of the dura and upward retraction of the cerebellum exposed the floor of the fourth ventricle for insertion of a wire or injection of silver nitrate solution. The wires and silver nitrate were placed as near as possible to the pressor areas of the medulla.[2] The areas richest in pressor cells were located by stimulating the ventricular floor with weak faradic current while the dog's femoral artery was attached to a recording mercury manometer. Most sensitive areas were on either side of the median sulcus in the region of the middle one third of the length of the ventricle.

Experiments and Results

1. *Simple Ligation of Vessels.* This procedure failed to produce hypertension lasting longer than 15 days.

A. In 5 animals the carotid and vertebral arteries were ligated at one operation. For several days afterward the animals behaved stupidly. They were dazed, apathetic, and listless, and often not interested in food or drink. Eventually, they recovered without obvious changes in habits or disposition. The blood pressures of these animals were above normal for two to three days (160 to 180 mm. Hg) and then reverted to normal (table 1 and fig. 1).

B. Forty-nine animals underwent two stage operations. In the first, one carotid, the vertebral, thyrocervical trunk, internal mammary, and costocervical arteries were ligated. The remaining carotid artery was cut three to six days later. Many of these animals were demented for days and often died. Of the 49, 20 died three to four days postoperatively, some without recovering from anesthesia. Of those that lived for a week or more, many had repeated convulsive seizures. Some had to be tube fed. They were untidy and wandered aimlessly about. Twenty-nine animals survived both stages of the operations and by the end of the tenth postoperative day they had resumed what seemed to be normal behavior patterns. Only 7 had significant hypertension which persisted for 8 to 15 days. A representative result is shown in figure 1 and table 1. For three to five days the blood pressure was 180 to 200 mm. Hg but thereafter it gradually decreased to become normal within two weeks.

Third stage operations were done on 10 of these animals in search for vessels large enough to be ligated. None was found. Arteriograms performed by injecting 70 per cent Diodrast into a brachial artery indicated why this was true. Myriad minute vessels coursing cephalad were visualized in the muscles of the neck (fig. 2).

In 10 animals we attempted to prevent the formation of these vessels or to obliterate them

Table 1.—*Incidence and Duration of Neurogenic Hypertension Induced by Various Means*

Method	Number Dogs			Dogs with Arterial Blood Pressure above 150 mm. Hg for 7 or more Days		Duration of Hypertension in Days
	Used	Lived				
		No.	Per cent	No.	Per cent	
Simple ligation of vessels.						
A. Carotid and vertebral arteries	5	5	100	0	0	2–3
B. All vessels	49	29	59	7	24	8–15
Ligation of vessels plus tantalum implant plus diathermy	22	14	64	9	64	60–300
Ligation of vessels plus sham craniotomy	14	10	71	2	20	7–24
Ligation of vessels plus injection of $AgNO_3$ into medulla	21	10	48	2	20	12–17
Ligation of vessels plus wire in 4th ventricle but without diathermy	25	12	48	4	33	45–90
Ligation of vessels plus diathermy but without wire implant						
A. Only carotid and vertebrals ligated	6	5	83	0	0	2–4
B. All vessels ligated	19	10	52	5	50	60–240

by pressure of scar tissue developed in response to bands of silk, cellophane or steel about the muscles of the neck. Bands were placed beneath the skin and included all of the neck tissue save the vagi, external jugular veins, the trachea, and esophagus. In spite of sterile precautions and the use of antibacterial drugs there was considerable tissue reaction with drainage from the operative site. Hence, probably more, rather than fewer, collateral vessels formed since none of these 10 dogs had significant hypertension.

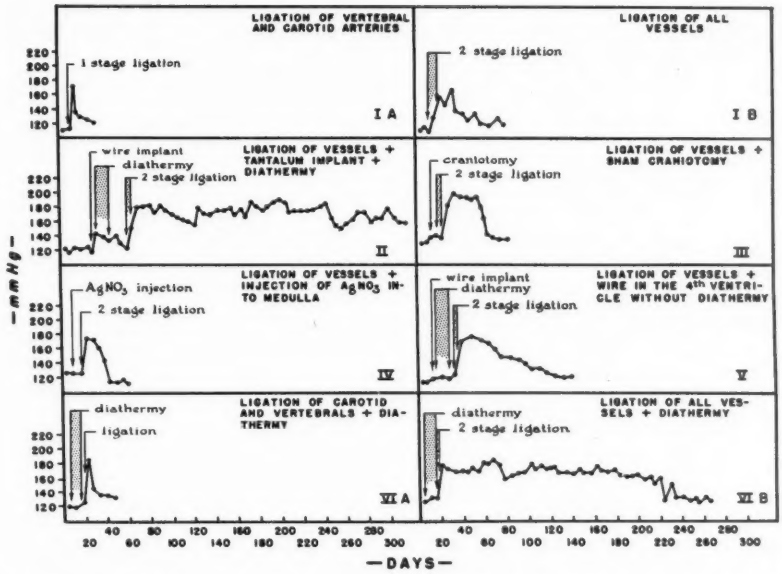


FIG. 1. Degree and duration of arterial hypertension following various neurogenic stimuli. Each solid dot represents the average blood pressures for a five day period. Those procedures which depended upon only cerebral ischemia produced hypertension of short duration. Combination of tantalum wire implant and ischemia gave a more prolonged hypertensive period as did the combination of diathermy and ischemia. The most sustained hypertension followed the combination of all three stimuli.

2. *Ligation of Vessels Combined with Tantalum Wire Implant in the Floor of the Fourth Ventricle and Diathermy.* As mentioned in the introduction, 2 dogs from a previous study developed prolonged hypertension after a combination of tantalum wire implant and 20 to 30 minutes of short-wave diathermy five to six days weekly for two to four weeks followed by ligation of the cerebral blood supply. The tantalum wire was inserted into the floor of the fourth ventricle through a suboccipital craniotomy. The wire was 1 cm. in length and was placed with a small forceps in the median raphe just below the ependymal layer so that it extended over the middle third of the ventricular floor. Twenty dogs were so prepared. Eight died following ligation of the vessels. Seven of the remaining 12 developed hypertension which lasted 2 to 10 months. Counting the 2 original animals, 9 of a total of 14 dogs that were subjected to wire stimulation, diathermy and surgically induced cerebral anemia had hypertension (170 to 180 mm. Hg) that lasted two months or longer (table 1 and fig. 1).

3. *Sham Craniotomy Combined with Ligation of Vessels.* Inasmuch as the dogs with wires in the fourth ventricle that had received diathermy were more apt to develop hypertension of longer duration than after either operation alone, experiments were performed to determine the more important mechanisms.

Fourteen animals were subjected to craniot-

omy following which the floor of the fourth ventricle was exposed and probed with a needle through the area usually receiving the tantalum wire. After six to eight days the cerebral blood vessels were ligated, following which 4 animals died. Only 2 of the remaining 10

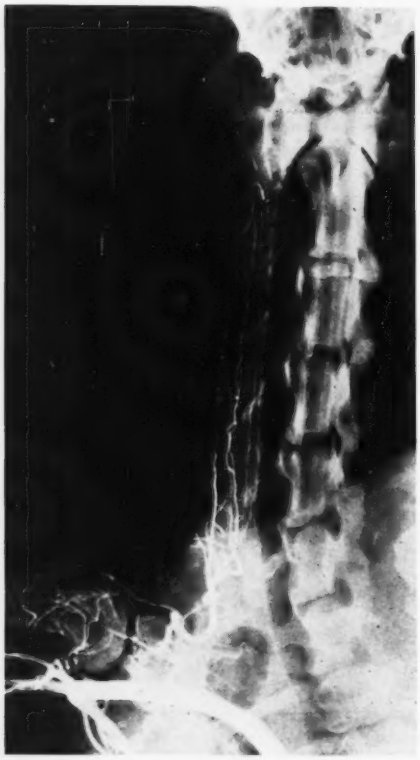


FIG. 2. This film of the right shoulder girdle and neck after retrograde injection of 70 per cent Diodrast into the brachial artery visualizes the right axillary and brachiocephalic arteries. The usual branches of these trunks have been ligated and are not seen. Arising from the vessels about the shoulder joint is an arterial trunk which sends many small branches cephalad through the neck muscles.

showed hypertension of any degree. This persisted but seven days in 1 and 24 days in the other. The results therefore did not differ from those following simple ligation of the vessels.

4. *Injection of Solutions of Silver Nitrate into the Fourth Ventricular Floor Combined with Ligation of Vessels.* This group of experiments was done to determine whether a chemical irritant acting in the region of the pressor areas along with ischemia might reproduce the hypertension following heating of a wire imbedded in the fourth ventricle. Twenty-one dogs were used. Suboccipital craniotomy was performed and the ventricular floor exposed. Various concentrations of silver nitrate solution were then injected into the region usually occupied by the tantalum wire. A 25 gage hypodermic needle was inserted below the ependyma much as were the bits of tantalum wire. As the needle was withdrawn, 0.25 cc. of three concentrations of silver nitrate were injected. Nine animals received 0.05 per cent solution; 9 received 0.1 per cent, and 3 received 0.2 per cent solution. However, none of the last 3 lived. At autopsy the brain stem was found to be almost completely destroyed and in a semisolid state. The 18 animals that lived underwent the second stage operation for ligation of the vessels six to eight days after craniotomy. Only 10 of these animals survived and of the 10 only 3 showed elevations of blood pressure (160 to 180 mm. Hg). However, at the end of 17 days all had normal blood pressures.

5. *Combination of Wire in Fourth Ventricle and Ligation of Vessels without Diathermy.* Neither sham craniotomy nor injection of silver nitrate into the region of the pressor areas before ligation of the vessels gave more significant hypertension than in otherwise normal dogs having surgically induced cerebral anemia. In the present group, the tantalum wire was placed and the cerebral circulation mechanically interrupted but diathermy was omitted. Twenty-five animals were used, only 12 of which lived. Four of these 12 developed hypertension lasting from one and a half to three months or slightly longer than dogs that had only ligation of the vessels.

6. *Ligation of Vessels Combined with Diathermy to the Head without Wire Implantation.* This group of experiments was performed to determine whether heating the brain of dogs with short-wave diathermy before, as well as following, restriction of the blood supply to the brain might influence the degree and duration of hypertension.

Twenty-five animals were given short wave diathermy to the head two days weekly two

to three weeks preoperatively and one to two weeks postoperatively.

A. Six dogs had ligation of only the vertebral and carotid arteries. One died. None of other 5 had significant hypertension.

B. Nineteen dogs had preoperative diathermy and ligation of all the blood vessels arising from the aortic arch and subclavian trunks. Nine of these died after the second operation for ligation of the final carotid artery, 5 had no hypertension but 5 showed moderate elevation of blood pressure (150 to 180 mm. Hg) that lasted two to eight months. A representative result is shown in figure 1. In this group, as with those with a wire in the fourth ventricle, hypertension was more sustained than in the previous experiments.

7. *Effects of Application of Heat to the Heads of Hypertensive Animals That Had Failed to Develop or Lost Hypertension.* In 6 animals that failed to develop hypertension and in 6 that began to lose their hypertension, heating of the head with short-wave diathermy was used in an attempt to induce or prolong hypertension. Although it was continued for four to eight weeks, the blood pressure remained within normal limits.

These experiments, which indicate that the combined effects of ischemia of the brain and mechanical and thermal stimulation of the medullary pressor areas often produce moderately prolonged neurogenic hypertension in dogs, made us wonder whether another type of neurogenic hypertension, that which accompanies elevation of intracranial pressure, was due entirely to pressure induced anemia as suggested by Cushing.[3] It seemed possible that in addition to anemia the mere pressure of the cerebrospinal fluid on the vasopressor areas might participate in inducing the peripheral arterial hypertension which accompanies cerebrospinal fluid hypertension. Two further groups of experiments were performed to explore this thesis.

8. *Ligation of All Vessels to the Brain Combined with Acute Cerebrospinal Fluid Hypertension.* Five animals were subjected to two stage ligation of the cerebral vessels. However, instead of ligating the second carotid, the vessel was simply exposed and clamped so that it could be released during subsequent studies. Three of these dogs had normal blood pressures, 1 had a control pressure of 178 mm. Hg, and the remaining dog had a pressure of 204 mm. Hg.

The cerebrospinal fluid pressure was now elevated by forcing saline with air pressure from a reservoir through a 15 gage needle, the tip of which was placed in the subarachnoid space by cisternal puncture. The pressure attained was measured by a mercury manometer connected into this system. The intracranial pressure (CSFP) was increased by increments of 10 to 20 mm. Hg. After the maximum elevation of pressure was noted the cerebrospinal fluid pressure was released and allowed to return to normal.

The rise of arterial blood pressure which occurred following elevation of cerebrospinal fluid pressure in dogs with cerebral ischemia was roughly proportional to the pressure applied to the brain. However, it varied widely from dog to dog and in the same animal at different times. Cerebrospinal fluid pressure of less than 60 mm. Hg had no effect. Cerebrospinal fluid pressure from 60 to 100 mm. Hg caused the arterial pressure to rise from 8 to 56 mm. Hg; pressure from 100 to 150 mm. Hg elevated arterial pressure from 50 to 128; pressure from 150 to 200 elevated arterial pressure 70 to 138 mm. Hg; and pressure from 200 to 250 produced a rise from 100 to 150 mm. Hg. Results of a typical experiment are shown in table 2.

If the intact carotid artery which had been clamped previous to the above experiments was released while the animals were hypertensive due to increased cerebrospinal fluid pressure, the blood pressure fell but not to the control levels. For instance, when the arterial pressure had been elevated from 144 to 238 mm. Hg by increasing the cerebrospinal fluid pressure to 150 mm. Hg, the release of the clamped carotid artery caused the blood pressure to fall to 190 mm. Hg. Reocclusion of the artery caused the blood pressure to rise to 228 mm. Hg.

The brains of these dogs had no major arterial blood supply, yet increased cerebrospinal fluid pressure caused a further elevation of arterial blood pressure. Although these data

suggest that the hypertension of increased intracranial pressure is due to both mechanical and anoxic stimulation of the pressor areas, we could not be certain the increased cerebrospinal fluid pressure was not simply obliterating the small vessels which kept the brain alive in spite of ligation of the larger vessels. To clarify this facet of the problem, four further experiments were performed.

TABLE 2.—*Representative Experiment of Effects of Progressive Elevation of Cerebrospinal Fluid Pressure of Dog with Cerebral Ischemia*

CSFP	Control Blood Pressure	Maximum Blood Pressure	Net Rise of Blood Pressure
mm. Hg	*mm. Hg*	*mm. Hg*	*mm. Hg*
40	176	172	−4
60	170	180	10
100	178	196	18
130	196	208	12
170	190	222	32
190	222	248	26
210	248	248	0
Effects of Acute Elevation of CSFP			
150	160	218	58
170	160	222	62
190	140	272	132
210	148	246	98
250	140	288	148
Effects of Occlusion and Release of Intact Carotid Artery during CSF Hypertension			
Procedure			
Occlude Carotid	144	182	38
CSFP 150 mm. Hg Carotid still occluded	182	238	56
CSFP 150 mm. Hg Carotid released	238	190	−48
CSFP released	190	116	−74
CSFP 150 mm. Hg Carotid open	116	178	62
CSFP 150 mm. Hg Carotid occluded	178	196	18
CSFP 150 mm. Hg Carotid released	196	170	−26
CSFP released	170	110	−60

9. *Effects of Cerebral Anemia and Increased Cerebrospinal Fluid Pressure in Animals with the Circulation of the Head Completely Isolated from That of the Body.* Four animals were prepared by a technic we describe in a forthcoming paper[4] so that the circulation of the brain was completely isolated from that of the body, the brain being perfused with the blood of a donor dog. In these animals the effects of complete cerebral anemia induced by clamping the donor arteries upon the arterial pressure of the body were compared with the effects of increased cerebrospinal fluid pressure.

When the perfusing artery was clamped, arterial pressure of the bodies of these 4 dogs rose sharply from control levels of 50, 54, 54 and 66 respectively* to a plateau at 80, 90, 184, and 194 mm. Hg. While the arteries were still clamped the cerebrospinal fluid pressure in the head was increased to 200 mm. Hg and the arterial pressure rose further to 120, 184, 208, and 234. Similar degrees of hypertension resulted when the cerebrospinal fluid pressure was elevated before clamping the donor arteries. If the arteries were not occluded no further rise in pressure occurred.

DISCUSSION

These experiments demonstrate that the additive pressor effects of ischemia of the brain and mechanical and thermal stimulation of the vasopressor areas of the medulla cause more prolonged arterial hypertension in a greater number of dogs than does any one of these procedures acting alone. Further, we have shown that the acute hypertension that attends elevation of cerebrospinal fluid pressure is not entirely due to ischemia of the brain resulting from pressure.[3] Rather, the mechanical effect of high cerebrospinal fluid pressure contributes in part to the systemic arterial hypertension which occurs.

Although these 165 experiments used, simultaneously, three agents each known to produce arterial hypertension of neurogenic origin of short duration, we have been unable to induce chronic elevation of blood pressure for longer than 10 months. The capacity of the dog to form collateral circulation rapidly counteracts ischemia of the brain while glial tissue soon

* The control blood pressures were low because the preparations had been used for several hours for other studies.

nullifies the mechanical stimulation arising from a wire in the medulla and insulates the pressor areas from heat generated in the wire by diathermy.

Since only 64 per cent of the animals prepared by combining all three methods developed hypertension, which lasted for periods varying from 2 to 10 months, the preparation has little value for chronic experimentation. This erratic behavior of the blood pressure of dogs receiving neurogenic pressor stimuli may well account for the observations made by Nowak and Walker[5] following ligation of the vertebral and carotid arteries, and by Fishback, Dutra and MacCamy[6] following progressive ligation of all arteries supplying the head. They all reported that such operations produced "chronic neurogenic hypertension." However, they used only a few animals and followed them for short periods of time. Likewise, the hypertension which Dixon and Heller[7] produced by injection of kaolin into the cisterna magna of rabbits was unimpressive and of very short duration. Indeed, many doubt that chronic hypertension can be produced by this method.

Regardless of the difficulties involved in the production of experimental neurogenic hypertension, it is evident that it can be induced so that it lasts nearly a year and might well continue indefinitely if the resourcefulness of nature did not compensate for the meddling of man.

Summary

One hundred and sixty-five dogs were used in a series of experiments designed to produce chronic hypertension of neurogenic origin. Surgically induced cerebral ischemia, which was severe enough to cause death in 41 per cent of the animals, induced arterial hypertension in only 24 per cent of those that lived and this lasted only 7 to 15 days.

If the effects of cerebral ischemia were augmented by the stimulation of a tantalum wire in the floor of the fourth ventricle heated by short wave diathermy, 64 per cent of the dogs developed hypertension (160 to 200 mm. Hg) which lasted 2 to 10 months.

Ischemia of the brain combined with the wire implant but without diathermy caused hypertension in 33 per cent of dogs which lasted 45 to 90 days. Ischemia plus diathermy to the head but without the wire implant caused hypertension in 50 per cent which lasted two to eight months.

The additive effects of cerebral anemia and mechanical stimulation were further demonstrated in animals with isolated, perfused brains in which total cerebral anemia could be produced by clamping a perfusing artery. In these animals the mechanical effects of increased cerebrospinal fluid pressure (150 to 200 mm. Hg) caused the systemic blood pressure which had previously risen maximally in response to complete anemia to become further elevated.

References

[1] Taylor, R. D.: The use of electromagnetic induction for the stimulation of nervous tissue in intact animals. Arch. Phys. Med. **28:** 626, 1947.

[2] Ranson, S. W., and Billingsley, P. R.: Vasomotor reactions from stimulation of the floor of the 4th ventricle. Studies in vasomotor reflex. Am. J. Physiol. **41:** 85, 1916.

[3] Cushing, H.: The blood pressure reactions of acute cerebral compression illustrated by cases of intracranial hemorrhage. Am. J. M. Sc. **125:** 1017, 1903.

[4] Taylor, R. D., and Page, I. H.: Peripheral vasomotor effects of adrenaline and noradrenaline acting upon the isolated perfused central nervous system. Circulation. In press.

[5] Nowak, S. J. G., and Walker, I. J.: Experimental studies concerning the nature of hypertension. Their bearing on surgical treatment. New England J. Med. **220:** 269, 1939.

[6] Fishback, H. R., Dutra, F. P., and MacCamy, E. T.: Production of chronic hypertension in dogs by progressive ligation of arteries supplying the head. J. Lab. & Clin. Med. **28:** 1187, 1943.

[7] Dixon, W. E., and Heller, H.: Experimentelle Hypertonie durch Erhöhung des intrakraniellen Druckes. Arch. f. exper. Path. u. Pharmakol. **166:** 265, 1932.

Cerebral Circulation and Metabolism in Uremia

By Albert Heyman, M.D., John L. Patterson, Jr., M.D., and Rudolph W. Jones, Jr , M.D.

Data on 16 patients with uremia are presented. The cerebral blood flow was moderately decreased in patients with generalized vascular disease, but was normal in patients with minimal vascular involvement. In both groups the cerebral oxygen consumption (cerebral metabolic rate in terms of oxygen consumption, $CMRO_2$) was reduced significantly and to the same degree. In contrast, total body metabolism was not demonstrably reduced. These facts emphasize the vulnerability of the brain to uremia. There was poor correlation between the cerebral oxygen utilization and the patient's mental state. No correlation was found between the cerebral oxygen consumption and the blood nonprotein nitrogen, the carbon dioxide capacity, or the sodium, potassium or chloride levels.

LITTLE information is available as to the specific factors responsible for the neurologic and mental symptoms associated with uremia.[1,2] The extensive histologic changes in the brain[3] and the increase in intracranial pressure sometimes seen in patients with the uremic syndrome may account to some extent for these neurologic abnormalities. With such changes, alterations in cerebral circulation and metabolism are to be anticipated.

This paper presents observations on the cerebral blood flow and oxygen consumption in 16 patients with uremia. An attempt is made to correlate alterations in these functions with the mental status of the patient, the etiology of the uremia, and the derangement of the chemical structure of the blood.

Case Material and Methods

The 16 patients in this study have been classified into two groups, depending on the presence or absence of generalized vascular disease and hypertension. In 9 patients the uremic syndrome was associated with evidence of extensive vascular disease and long-standing severe hypertension. The mean arterial blood pressure in these 9 patients varied from 129 to 203 mm. Hg and averaged 166 mm. These patients had advanced retinal arteriosclerosis, usually with hemorrhages and exudates and, occasionally, papilledema. The diagnosis in 4 of these patients was chronic glomerulonephritis; in 5 others, malignant nephrosclerosis. The uremic syndrome in the other group of 7 patients was not associated with extensive vascular disease. Two of them had hydronephrosis caused by lower urinary tract obstruction, one had lower nephron syndrome of unknown etiology, while 4 had chronic pyelonephritis. Two of the patients with pyelonephritis had moderate hypertension of recent duration and showed some abnormalities of the retinal vessels. The remaining 5 patients in this group had normal blood pressures with only slight or no evidence of vascular disease. These 7 patients are, for convenience, referred to subsequently as the "group without vascular disease." The mean age of the patients in these two groups was approximately the same, averaging 43 years. The blood nonprotein nitrogen, hemoglobin, carbon dioxide capacity, serum sodium and plasma chloride levels were likewise similar. The serum potassium level was slightly higher in the group of patients without vascular disease.

The 16 individuals used as control subjects had an average age of 34 years and comprised patients who were convalescing from various acute illnesses, such as pneumonia and gonococcal arthritis. There was no evidence of intracranial complication in any of these patients. Both the control subjects and the patients with uremia had normal temperatures at the time of the cerebral studies. The determinations were made with the subjects in the supine position. If the patient was restless or uncooperative during the blood flow procedure, or if the control subject showed undue anxiety, the determination was rejected as invalid.

The cerebral blood flow (CBF) was measured by the nitrous oxide technic of Kety and Schmidt[4] with the slight modifications previously described.[5] The cerebral oxygen consumption ($CMRO_2$) was calculated from the cerebral blood flow and the cerebral arteriovenous oxygen difference determined manometrically.[6] The cerebral vascular resistance (CVR) was calculated from the cerebral blood flow

From the Departments of Medicine and Physiology, Emory University School of Medicine, and the Medical Service of Grady Memorial Hospital, Atlanta, Ga.

and the mean arterial pressure was measured directly with a damped mercury manometer. Total oxygen consumption of the body was measured by the open circuit technic. The basal metabolic rate was calculated from the oxygen consumption and carbon dioxide production according to the formula given by Weir.[7] A group of 41 subjects studied under similar experimental circumstances were used as controls for this determination. The blood nonprotein nitrogen level was determined by the Koch-McMeekin method[8]; serum concentrations of sodium and potassium were measured with the flame photometer. The plasma chloride level was determined by the method described by Schales and Schales,[9] and the carbon dioxide combining power by conventional manometric technic.

Results

The individual and mean values obtained in the patients with uremia and in the control subjects are shown in table 1 and figure 1. The mean cerebral blood flow in the 16 patients with uremia was only slightly less than normal and measured 52 cc. per 100 Gm. brain per minute ($.1 > p > .05$). In the 9 patients with uremia associated with generalized vascular disease, however, the mean cerebral blood flow was 45 cc., a value significantly less than that of the control subjects ($p < .01$). The uremic patients without generalized vascular involvement had a mean cerebral blood flow value approximately the same as normal individuals.

All but one of the 16 patients with uremia had cerebral oxygen consumption values below the normal mean and the values of only 4 were within the normal range (fig. 1). The mean cerebral oxygen utilization in these patients was only 2.2 cc. per 100 Gm. per minute, a value significantly less than that of 3.1 cc. found in the control subjects ($p < .001$). The patients with uremia associated with generalized vascular disease had a greater cerebral arteriovenous oxygen difference (5.1 volumes per cent) than those without vascular involvement (4.1 volumes per cent). The cerebral oxygen consumption in these two groups was consequently the same despite the differences in cerebral blood flow.

Little correlation was observed between the level of the blood nonprotein nitrogen and the cerebral oxygen utilization value (figure 2). Neither the anion-cation pattern as measured nor the individual values for carbon dioxide capacity, sodium, potassium and chloride levels showed a correlation with the cerebral oxygen consumption.

The total oxygen consumption in the 7 patients with uremia, on whom this determination was made, average 137 cc. per square meter per minute, or only 4 per cent below that of control subjects. The mean basal metabolic rate was 4 per cent above the mean value predicted from the standards of DuBois. The cerebral oxygen consumption in these 7 patients, however, was reduced to a rather marked degree, i.e., 30 per cent below that of the control subjects.

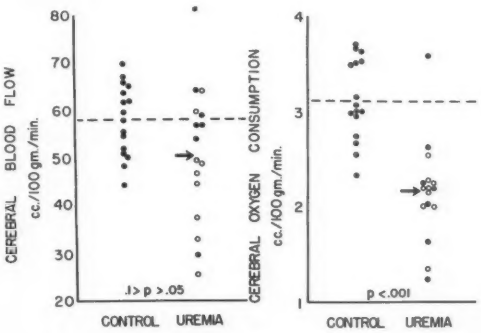


FIG. 1. The values for cerebral blood flow and oxygen consumption in the individual patients. The arrows indicate the mean value in each group. The dotted lines represent the mean values in the control subjects. The open circles denote uremia patients with hypertension and vascular disease; the solid dots, the uremia patients without generalized vascular disease.

The 9 patients with uremia associated with vascular involvement had a cerebral vascular resistance of 3.9 mm. per cc. per 100 Gm. per minute, a value more than double those found in the control subjects ($p < .001$), and in the uremic patients without vascular disease ($p < .001$). This increase in vascular resistance did not correlate with the patients' retinal findings. The 3 patients with papilledema and marked retinopathy did not have the highest cerebral vascular resistance values, but did show the highest blood pressure levels.

Results of Repeated Studies in Individual Patients. Repeated cerebral studies were carried out in 3 patients during the course of their

TABLE 1.—*Clinical, Chemical and Physiologic Data on 16 Patients with Uremia*

Pt.	Diagnosis	Age	Mental Status	Retinal Arteriosclerosis	Mean Art. Pressure mm./Hg	CBF cc./100 Gm./ Min.	$CMRO_2$ cc./100 Gm/ Min.	CVR mm. Hg/cc./100 Gm./min.	Total O_2 Consumption cc./sq. m./min.	A-VO_2 Vol. %	NPN mg. %	CO_2 Capacity mEq./l	Chlorides mEq./l.	Sodium mEq./l.	Potassium mEq./l.	Hemoglobin Gm. %	Hematocrit
Uremia Associated with Severe Hypertension and Vascular Disease																	
G. D.	Malig. nephrosclerosis*	43	Stuporous	Severe P.H.E.	203	60	2.2	3.4	95	3.7	225	14	84	128	5.0	12.5	36
R. B.	Malig. nephrosclerosis	48	Stuporous	Severe P.H.E.	195	37	2.3	5.2	—	6.2	87	10	—	—	—	12.7	40
H. S.	Malig. nephrosclerosis	34	Stuporous	Severe H.E.	161	47	2.0	3.5	—	4.3	276	10	82	129	3.4	8.5	28
M. T.	Malig. nephrosclerosis*	50	Alert	Severe P.H.E.	184	64	2.2	2.9	144	3.4	78	21	93	148	3.4	9.3	27
F. W.	Malig. nephrosclerosis*	36	Alert	Severe H.E.	175	45	1.4	3.9	—	3.0	126	16	—	—	—	8.1	24
B. G.	Glomerulonephritis	50	Stuporous	Moderate	130	49	2.6	2.7	—	5.2	200	10	107	136	4.7	10.0	31
M. S.	Glomerulonephritis	48	Sl. confused	Severe	155	26	2.0	6.1	113	7.9	105	23	82	135	3.7	12.4	46
L. W.	Glomerulonephritis	47	Confused	Severe H.E.	129	49	2.2	2.6	—	4.4	105	18	100	134	4.8	9.2	—
A. P.	Glomerulonephritis*	39	Confused	Severe H.E.	165	30	2.3	5.5	—	7.5	218	16	—	112	4.2	9.1	33
Mean Values		44			166	45†	2.1†	3.9†,‡	117	5.1	158	15	92	132	4.2	10.2	33
Uremia without Prolonged Hypertension and Generalized Vascular Disease																	
F. B.	Pyelonephritis	41	Stuporous	Moderate H.	—	60	2.2	—	—	3.5	180	—	110	132	2.9	6.5	15
R. F.	Pyelonephritis	20	Confused	Normal	111	57	2.0	2.0	198	3.6	143	19	96	132	5.0	9.2	26
A. G.	Hydronephrosis*	49	Stuporous	Normal	110	59	1.2	1.9	135	2.1	289	10	100	142	5.8	8.9	24
H. H.	Pyelonephritis	63	Confused	Moderate	134	54	1.6	—	90	3.1	121	10	114	145	7.1	8.8	20
A. M.	Pyelonephritis*	31	Alert	Moderate	132	57	2.6	2.3	184	4.6	153	12	114	137	7.3	12.8	37
C. M.	Prostatic obstruction	52	Sl. confused	Mild	104	81	3.6	1.3	—	4.4	96	16	—	134	6.4	11.2	32
P. T.	Lower Nephron disease	35	Unconscious	Normal	42	30	2.3	1.4	—	7.4	132	24	60	137	2.8	10.7	32
Mean Values		42			100	57	2.2†	1.8	152	4.1	159	15	99	137	5.3	9.7	27
16 Control Pts.		34	Normal	Normal	105 ± 22§	58 ± 7	3.1 ± .4	1.8 ± .4	140 ± 24.9	5.5 ± .9							

P = papilledema.
H = hemorrhages.
E = exudates.
* Diagnosis confirmed by autopsy or surgical exploration.
† Statistically significant difference ($p < .01$) from mean value in control patients.
‡ Statistically significant difference from mean value in patients without prolonged hypertension and generalized vascular disease.
§ Standard Deviation.

illnesses (table 2). One of them (G.D.), with malignant nephrosclerosis, was studied early in the course of his illness, when there was no evidence of uremia other than an elevation of nonprotein nitrogen to 78 mg. per 100 cc. The cerebral oxygen utilization was normal at this time, but was decidely reduced a month later when he returned in uremic stupor with a marked increase in nonprotein nitrogen. In another patient (A.G.), the clinical manifestations of uremia disappeared following bilateral nephrostomy of hydronephritic kidneys. This patient showed a gradual elevation in cerebral oxygen consumption along with a reduction in nonprotein nitrogen and improvement of mental function. The third patient (B.G.) had chronic glomerulonephritis. She eventually developed a remission of uremic symptoms with marked reduction in nonprotein nitrogen and improvement in mental state. The clinical improvement was associated at first with a slight rise in both cerebral blood flow and cerebral oxygen utilization, but these values later decreased without a corresponding change in the mental picture. There were no consistent changes in the cerebral blood flow in these individuals. With a single exception the cerebral vascular resistance remained remarkably constant.

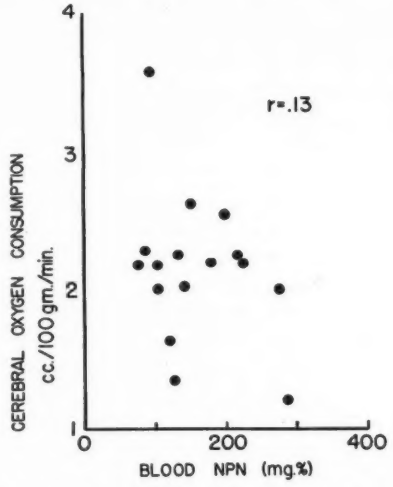


FIG. 2. The relationship between cerebral oxygen consumption and blood nonprotein nitrogen.

There appeared to be considerably less correlation between mental state and cerebral oxygen consumption in the entire group of patients with uremia. The mean and the distribution of

TABLE 2.—*Clinical and Experimental Data Obtained in Repeated Studies in Three Patients with Uremia*

	G.D., Malignant Nephrosclerosis		A.G., Hydronephrosis				B. G., Chronic Glomerulonephritis		
	8/12/49	9/9/49	11/9/49	11/18/49	12/13/49	4/17/50	5/12/49	1/18/50	4/14/50
CBF, cc./100 Gm./min.	55	60	59	42	51	60	49	58	45
$CMRO_2$, cc./100 Gm./min.	3.5	2.2	1.2	1.3	1.5	2.2	2.6	2.9	2.1
CVR—mm. Hg/cc./100 Gm./min.	3.4	3.4	1.9	2.1	2.1	2.1	2.7	1.8	2.6
Mean arterial pressure mm. Hg	189	203	110	87	105	127	130	104	134
NPN mg.%	78	225	289	195	119	97	200	36	40
CO_2 Cap. mEq./l.	22	14	10	22	17	10	10	19	24
Chlorides mEq./l.	—	84	100	95	101	114	107	109	109
Sodium mEq./l.	132	128	142	141	139	138	136	137	139
Potassium mEq./l.	3.7	5.0	5.8	4.8	5.2	4.0	4.7	4.8	5.0
Hemoglobin Gm.%	10.9	12.5	8.9	7.1	10.1	6.8	10	11.1	10.6
Mental Change	Alert	Stupor	Stupor	Stupor	Sl. confused	Alert	Confused	Sl. confused	Alert

the cerebral oxygen utilization values were very similar in the patients classified as being alert, confused or stuporous (fig. 3).

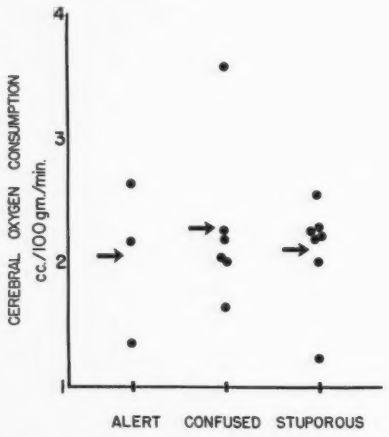


FIG. 3. The mean values for cerebral oxygen consumption grouped according to the mental state of the patients with uremia. The arrows indicate the mean value in each group.

DISCUSSION

These studies demonstrate that uremia is often associated with a profound depression in cerebral metabolism. The normal mean cerebral blood flow value in the group of uremic patients without vascular disease suggests that, in these patients at least, the decrease in cerebral oxygen consumption must have been caused by factors other than reduction in blood flow. However, in the presence of anemia of the degree found in some of these patients, it is quite possible that a "normal" blood flow could be inadequate for the needs of the brain. As previously stated, no definite correlation could be made between the reduction in cerebral oxygen consumption and the carbon dioxide capacity, nonprotein nitrogen and concentrations of sodium or potassium. It is possible that some of the other alterations associated with uremia, such as changes in pH, increase in phenolic substances in the blood, could have been responsible for the changes in cerebral functions. It seems as likely, however, that the reduction in cerebral oxygen utilization was not dependent on any single factor, but was the result of the combined effect of a number of chemical disturbances.

The fact that there was a marked reduction of cerebral oxygen consumption in uremia, whereas a depression in total body metabolism was not demonstrated, emphasizes the vulnerability of nervous tissue to this condition. However, some of the patients with chronic renal insufficiency showed relatively normal mental function, despite low cerebral oxygen utilization values. This was particularly noticeable in the 2 patients who had remissions of the uremic syndrome. Although these individuals regained considerable mental function, their cerebral oxygen consumption values remained well below normal. Kety and associates,[10] from studies on patients with diabetic acidosis, suggested that there exists a critical cerebral oxygen utilization of 2.1 cc. per 100 Gm. per minute, at or below which consciousness disappears. It is of interest that several of our patients with uremia, while conscious, showed oxygen consumption values lower than this figure. Similar findings were obtained in our patients with dementia paralytica.[5] It appears, therefore, that such a critical cerebral oxygen consumption, if it does exist, must vary with the nature of the disease.

The effects of specific chemical alterations on cerebral metabolism in uremia could possibly be determined by a more comprehensive study including selective correction of the various electrolyte derangements and removal of certain metabolites by means of artificial excretory mechanisms. These procedures might suggest methods of alleviating the cerebral dysfunction, which appears to be the cause of death in many of these patients. Further work in this direction seems desirable.

SUMMARY

1. The cerebral blood flow (CBF), oxygen consumption ($CMRO_2$) and cerebral vascular resistance (CVR) were determined by the nitrous oxide technic in 16 patients with uremia caused by a variety of conditions.

2. A moderate decrease in cerebral blood flow was found in patients with uremia associated with severe hypertension and generalized vascular disease. The uremic patients with little

or no vascular involvement had a normal mean cerebral blood flow value.

3. The cerebral oxygen consumption in uremia was significantly reduced. This decrease was as marked in patients with normal cerebral blood flow as in those with reduced blood flow. A decrease in total body metabolism was not demonstrated. This suggests that nervous tissue is especially vulnerable to the effects of renal insufficiency.

4. In general, poor correlation was observed between the degree of reduction in cerebral oxygen utilization and the mental state of the patient with uremia. In some patients with uremia the cerebral metabolism was considerably reduced without marked impairment of mental function.

5. No correlation was found between the degree of reduction in cerebral oxygen consumption and the level of the blood nonprotein nitrogen, the carbon dioxide capacity or the sodium, potassium or chloride levels.

ACKNOWLEDGEMENTS

We are indebted to Misses Fransetta Vinson, Voncile Williams, Mary McPhaul, and Mary Upshaw for their technical assistance.

REFERENCES

[1] BRADLEY, S. E.: Biochemical abnormalities during renal insufficiency. New England J. Med. **235:** 755, 791, 1946.

[2] HARRISON, T. R., AND MASON, M. F.: The pathogenesis of the uremic syndrome. Medicine **16:** 1, 1937.

[3] KNUTSON, J., AND BAKER, A. B.: The central nervous system in uremia. Arch. Neurol. & Psychiat. **45:** 130, 1945.

[4] KETY, S. S., AND SCHMIDT, C. F.: The nitrous oxide method for the quantitative determination of cerebral blood flow in man. Theory, procedure and normal values. J. Clin. Investigation **27:** 476, 1948.

[5] PATTERSON, J. L., JR., HEYMAN, A., AND NICHOLS, F. T., JR.: Cerebral blood flow and oxygen consumption in neurosyphilis. J. Clin. Investigation. **29:** 1327, 1950.

[6] PETERS, J. P., AND VAN SLYKE, D. D.: Quantitative Clinical Chemistry. Vol. II. Methods. Baltimore, Williams & Wilkins, 1943 (emended edition).

[7] WEIR, J. B. DE V.: New methods for calculating metabolic rate with special reference to protein metabolism. J. Physiol. **109:** 1, 1949.

[8] KOCH, F. C., AND MCMEEKIN, T. L.: A new direct nesslerization micro-Kjeldahl method and a modification of the Nessler-Folin reagent for ammonia. J. Am. Chem. Soc. **46:** 2066, 1924.

[9] SCHALES, O., AND SCHALES, S. S.: A simple and accurate method for the determination of chloride in biological fluids. J. Biol. Chem. **140:** 879, 1941.

[10] KETY, S. S., POLIS, B. D., NADLER, C. S., AND SCHMIDT, C. F.: The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. J. Clin. Investigation **27:** 500, 1948.

The Electrocardiogram in Congenital Heart Disease

A Preliminary Report

By Oglesby Paul, M.D., Gordon S. Myers, M.D., and James A. Campbell, M.D.

Adequate unipolar electrocardiograms have been recorded on 101 patients with congenital heart disease and the findings analyzed. It has been found that the chief value of such tracings rests in the determination of ventricular preponderance, the evidence being obtained from study of the QRS complexes in unipolar limb and multiple precordial leads, with relatively little help from the RS-T segments and T waves. Auricular hypertrophy, encountered chiefly in association with pulmonic stenosis and tricuspid valve disease, could be best detected by analysis of P waves seen in the right precordial leads rather than in the limb leads. Intraventricular block was observed both with auricular and with ventricular septal defects, and was also found in Ebstein's disease and with coarctation of the aorta. Auriculoventricular block and arrhythmias were rare.

ACCURATE diagnosis of congenital cardiac lesions no longer must await evidence supplied at the autopsy table. Today, in the majority of such cases, specific and precise data as to the nature of single or multiple cardiovascular anomalies can be obtained as the result of a careful assessment of clinical and laboratory findings. It is well known that the history and physical examination by themselves are often inadequate to provide a satisfactory diagnosis; and information secured through roentgenologic study, including angiocardiography, and cardiac catheterization, including blood gas analysis, are necessary in many instances. The electrocardiogram is an additional and valuable laboratory tool. It does not by itself provide a final answer, except in instances of uncomplicated dextrocardia of the situs inversus type, but it does indicate whether gross preponderance and hypertrophy of the right or left ventricles exist, whether there is evidence of auricular hypertrophy, and whether abnormalities of rhythm or conduction are present.

The analysis of electrocardiographic tracings in the congenital cardiac group is not altogether easy. In order to obtain maximum help in determining the presence of an abnormal right or left ventricular preponderance, at least three and preferably more precordial leads should be available; in this regard, the unipolar limb leads are of value as a guide to the electrical position of the heart. Furthermore, while it is not difficult to detect abnormally high voltage of the QRS complexes in adults, it is a different matter in infants and young children, where the thinness of the chest wall and proportions of the heart and thoracic cage are such that relatively high voltage complexes may normally be found. Reliable standards for the normal P and QRS amplitudes have not been fully established for this age group. It is also well known that a vertical or a mild right axis deviation is a more common finding in normal infants and children than in adults, and in the past an undue and unjustified emphasis has been placed on axis deviation as such. It is our belief that the significance of axis deviation should be considered in the light of other findings in the limb and chest leads.

The following data has been obtained by analysis of the electrocardiograms of 101 patients with congenital cardiovascular lesions ranging in age from 1 day to 52 years (53 of the group were over the age of 12 years). The

From the Massachusetts General Hospital, Boston, Mass. and the Presbyterian Hospital, Chicago, Ill.

Presented at the Twenty-third Annual Scientific Sessions of the American Heart Association held in San Francisco, Calif., June, 1950.

diagnoses (table 1) have been confirmed in 96 patients by cardiac catheterization, surgical exploration, autopsy findings, or by a combination of these methods. In 5 instances (1 case of dextrocardia with situs inversus and 4 cases of aortic or subaortic stenosis) this type of proof as to the nature of the lesion is not at hand; however, precise clinical observations are available.

TABLE 1.—*Diagnoses in 101 Patients with Congenital Cardiac Anomalies*

	No. of Cases
Patent Ductus Arteriosus	24
Tetralogy of Fallot	15
Ventricular Septal Defect	11
Coarctation of the Aorta	11
Pulmonic Stenosis, Isolated	8
Pulmonic Stenosis & Auricular Septal Defect	7
Auricular Septal Defect	5
Subaortic or Aortic Stenosis	4
Auricular & Ventricular Septal Defects	3
Dextrocardia with Situs Inversus	2
Dextrocardia without Situs Inversus	2
Pulmonic Stenosis & Aortic Regurgitation	2
Transposition Great Vessels	2
Ebstein's Disease	1
Coronary Arteriovenous Fistula	1
Patent Ductus Arteriosus with Mitral Valvulitis	1
Tricuspid Atresia	1
Tricuspid Stenosis, Pulmonic Stenosis, Patent Foramen Ovale, Endocardial Sclerosis Right Ventricle	1
Total	101

Standard limb leads, augmented unipolar limb leads, and at least three unipolar chest leads were recorded in each case.

DEXTROCARDIA

The diagnosis of uncomplicated dextrocardia of the situs inversus type is readily made by examination of the electrocardiogram. The findings are absolutely characteristic and, if chest leads are available, cannot be confused with any other entity. There is seen a total inversion of lead I. Leads II and III appear to have been interchanged as do leads aV_R and aV_L, and the precordial leads taken in the usual fashion show an absence of the normal QRS progression, with small complexes as one approaches the left axilla. However, precordial leads recorded over the right side of the thorax are quite normal in appearance.

Dextrocardia without situs inversus and without other anomalies is occasionally encountered and in such cases the standard and unipolar limb leads are essentially within normal limits. The precordial leads are also normal, except that they may show a shift of the QRS transitional zone to the right.

AURICULAR SEPTAL DEFECT INCLUDING LUTEMBACHER'S SYNDROME

McCulloch[1] in 1916 published the electrocardiogram of a 23 month old infant whose heart showed at autopsy a large auricular septal defect. This tracing was characterized by right axis deviation with peaked P waves in leads II and III. In 1934, Roesler[2] discussed the problem of auricular septal defect at length, citing 62 cases, 5 of which were studied with apparently adequate electrocardiograms. Four of these revealed a moderate right axis deviation and 1 showed a marked right axis deviation. Bedford, Papp, and Parkinson[3] in their 1941 article include 10 cases proved at autopsy. In their uncomplicated septal defect group, there were no arrhythmias and most of the tracings showed a right axis deviation. Their cases of auricular septal defect associated with mitral stenosis (Lutembacher's syndrome) were characterized electrocardiographically by the presence of auricular fibrillation or flutter with right axis deviation, and one is stated to have shown a right bundle branch block. Brown[4] has reported that a slight right axis deviation is common and that the P waves may be large, and Taussig,[5] remarking that right axis deviation is "the rule" and that the P waves are high, adds that the P-R interval is frequently prolonged and that notching and widening of the QRS complexes may occur. A right axis deviation was observed in the electrocardiograms of 3 of 4 patients with this diagnosis studied by Brannon, Weens and Warren,[6] and the tracing of the fourth showed a tendency to right axis deviation.

We have studied 5 patients with auricular septal defects, all diagnosed by cardiac catheterization, and believe that on clinical grounds 3 are associated with mitral stenosis. The age

range of this group was 8 to 30 years. Four of the 5 patients were males. No arrhythmias were seen. The most significant findings in the electrocardiograms were the presence of right bundle branch block in 2 cases (the intraventricular conduction times measured 0.12 second), right axis deviation (+120°) in a third accompanied by a right bundle branch block pattern in the precordial leads but with normal QRS duration, and similarly right axis deviation (+125°) in a fourth case with precordial leads consistent with right ventricular hypertrophy. The electrocardiogram in the fifth patient revealed a vertical axis but did not suggest enlargement of the right ventricle and no block was present. The P waves were normal in 1 tracing and in 4 others were peaked and slightly high (0.15 to 0.2 millivolt) in leads V_1, and/or V_2 (and in 1 case V_3 and V_4).* In no instance were the P waves strikingly abnormal and no A-V block was seen. The QRS voltages were not remarkable.

Figure 1 illustrates an electrocardiogram on a 16 year old male with an uncomplicated auricular septal defect, showing a characteristic right bundle branch block.

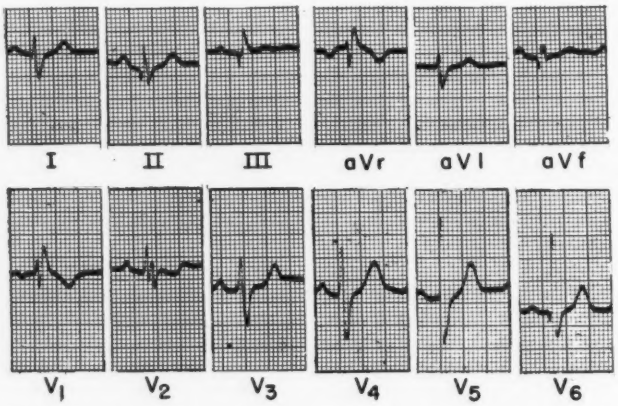


FIG. 1. Electrocardiogram of a 16 year old male with uncomplicated auricular septal defect, showing a characteristic right bundle branch block.

* We have reviewed a series of electrocardiograms recorded on normal children and adults and have observed that the P waves do not exceed 0.15 millivolt in amplitude in unipolar precordial leads.

VENTRICULAR SEPTAL DEFECT

In no aspect of the field of congenital heart disease may such wide clinical, x-ray, and electrocardiographic variations be found as in lesions of the ventricular septum. Despite our textbook concepts, the "simple" ventricular septal defect (Roger's disease) often blends into Eisenmenger's complex, and the latter, in turn, in its advanced form, may be difficult to distinguish from cor triloculare biatriatum unless the heart is examined for disease. For this reason, we are grouping all lesions of the ventricular septum under one main heading but we will refer to the classic subgroup diagnoses arrived at through the use of the various clinical and laboratory methods at our disposal.

The "simple" ventricular septal defect is stated to be characterized by a normal electrocardiogram.[4, 5] Electrocardiograms reported on patients with Eisenmenger's complex have often shown right axis deviation, at times a right bundle branch block, and prominent P waves.[4,7–9] Cor triloculare biatriatum may also give a tracing with large P waves and intraventricular block.[10]

Our present series includes 4 noncyanotic patients, all studied by cardiac catheterization, who have been shown to have ventricular septal defects probably best labeled as Roger's

lisease. The age range was from 6 to 11 years and three were females. Except for left axis deviation (−20° and −47°) in 2 of the tracings, the electrocardiograms showed no characteristic findings and in particular no intraventricular block was seen.

We have also seen 4 patients (3 studied by cardiac catheterization and 1 by angiocardiography and later by operation) with ventricular septal defects which might be classified as Eisenmenger's complex. Three of these patients were cyanotic with low arterial oxygen saturations, and the fourth, although not cyanotic, had an arterial oxygen saturation of 86 per cent. All showed clubbing and prominent pulmonary vessels on fluoroscopy. The youngest was 6 years of age and the oldest was 43. All of these had electrocardiograms characterized by a right axis deviation. Three tracings showed the picture of right ventricular hypertrophy in the precordial leads (fig. 2), one being associated with the right bundle branch block pattern without actual QRS prolongation, and another revealing definite intraventricular block (QRS duration of 0.12 second) of an indeterminate type. A mixed QRS progression of uncertain significance was found in the precordial leads of the fourth patient. Variable A-V block with at times a nodal rhythm was noted in one electrocardiogram but the P waves were otherwise abnormal in only one record in which high peaked P waves were seen in leads II, III, and aV_F with deeply inverted P waves in V_2 and upright peaked P waves in V_4.

Also to be included in this group are 3 patients, 2 diagnosed as cor triloculare biatriatum (one aged 1 day studied at autopsy, and one aged 25 years diagnosed by cardiac catheterization), and one aged 8 years, diagnosed also by cardiac catheterization as having a huge ventricular septal defect. Prominent P waves, usually peaked, were observed in two of the three tracings in the limb and precordial leads. A complete right bundle branch block was found in one, a probable incomplete left bundle branch block in another, and a high degree of right axis deviation (+150°) with precordial leads indicative of right ventricular preponderance was present in the infant's electrocardiogram. The voltage of the QRS complexes was increased in two of the tracings.

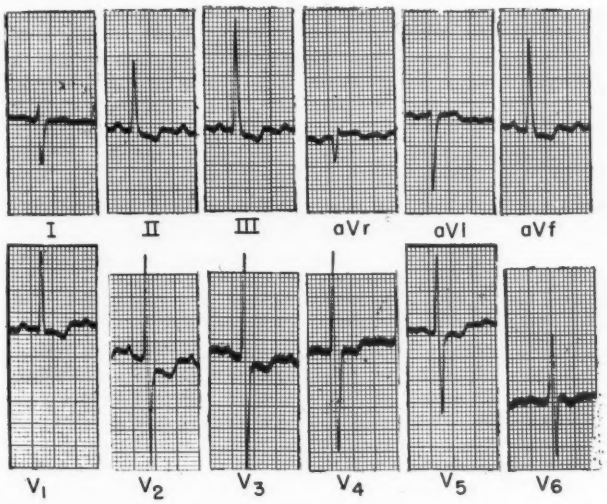


FIG. 2. Electrocardiogram of a 43 year old female with Eisenmenger's complex, showing right axis deviation, a right ventricular hypertrophy pattern in the precordial leads, and slight prolongation of the intraventricular conduction time.

Combined Auricular and Ventricular Septal Defects

Our 3 examples of combined auricular and ventricular septal defects were 3 month and 14 month old male infants, both studied at autopsy, and a 6 year old girl who was diagnosed by cardiac catheterization. The electrocardiograms taken on these patients were not distinctive, except that two showed slightly prominent P waves, and all three had a vertical axis. The precordial leads indicated an essentially balanced bilateral ventricular hypertrophy in 2 cases, which was confirmed at autopsy, and in the third case bilateral ventricular hypertrophy was evident but with preponderance of the left ventricle. There was no auriculoventricular or intraventricular block present and there were no arrhythmias.

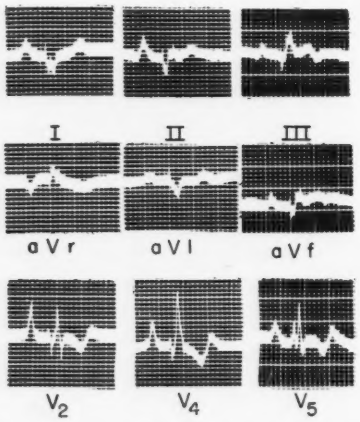


Fig. 3. Electrocardiogram of a 16 year old male with Ebstein's disease, characterized by right bundle branch block and very high peaked P waves.

Ebstein's Disease

Few cases of Ebstein's disease (congenital downward displacement and deformity of the tricuspid valve) have been reported. The electrocardiogram of the patient described by Yater and Shapiro[11] was characterized by intraventricular block, probably left bundle branch block, with paroxysms of supraventricular tachycardia. The 3 cases reported by Engle, Payne, Bruins, and Taussig[12] showed high peaked P waves, A-V block, and right bundle branch block in 2 patients (and probably also in the third).

Our patient with Ebstein's disease, a 16 year old boy whose heart was examined pathologically, also had right bundle branch block in his electrocardiogram (fig. 3), the intraventricular conduction time measuring 0.12 second. Very high peaked P waves were found, being especially prominent in the precordial leads, and it was seen at autopsy that these were related to a greatly enlarged right auricle. No septal defect was present.

Tricuspid Atresia

The clinical diagnosis of tricuspid atresia depends to an unusual extent upon the presence of characteristic electrocardiographic findings. Blackford and Hoppe[13] in 1931, and Taussig[14] in 1936, commented upon the presence of a left axis deviation as a most valuable distinctive feature, serving to differentiate this group of cyanotic patients with a small right ventricle, from the much larger cyanotic group associated with right ventricular hypertrophy.

We have seen one such patient, a young woman aged 24 years, in whom the clinical impression of tricuspid atresia was confirmed by cardiac catheterization. Her electrocardiogram (fig. 4) showed a left axis deviation of high degree, broad, high, notched P waves, and slight prolongation of the intraventricular conduction time (QRS, 0.11 second). The voltage of the qR complex in lead aV_L was slightly increased, and the precordial leads were characteristic of left ventricular preponderance.

Isolated Pulmonic Stenosis

In 1945, Currens, Kinney, and White[15] reported the findings in a series of 11 cases of pulmonic stenosis with an intact ventricular septum. Electrocardiograms were available on 4 of these, three of which showed a marked right axis deviation (1 of these cases had a good-sized patent foramen ovale) whereas the fourth, recorded on a 43 year old patient with only moderate stenosis, showed a normal axis. On reviewing the tracings, it is seen that the P waves tend to be high and peaked, and that in 2 instances, a definite T_2 and T_3 inversion

is present with some RS-T segment depression and sagging. Greene and co-workers[16] have described 4 patients with pure pulmonic stenosis and observed that a right axis deviation was present in only 1 of the 4; it is of interest that this one patient, although the youngest in the group, had the highest right ventricular systolic pressure. Blackford and Parker[17] have reported a case of a 23 year old male with uncomplicated pulmonic stenosis whose electrocardiogram, limited to the three standard limb leads, showed an apparent complete right bundle branch block with a high peaked P_2 and P_3.

right axis deviation was observed in the 3 others. The precordial leads were characteristic of right ventricular hypertrophy in five electrocardiograms and suggestive in a sixth, but only 1 of these showed RS-T and T wave abnormalities of the typical right ventricular "strain" type.

This evidence of a right ventricular preponderance could be correlated with the right ventricular pressures observed at the time of cardiac catheterization. In the 2 instances in which the resting right ventricular systolic pressure was less than 50 mm. Hg, the QRS progression in the precordial leads was normal

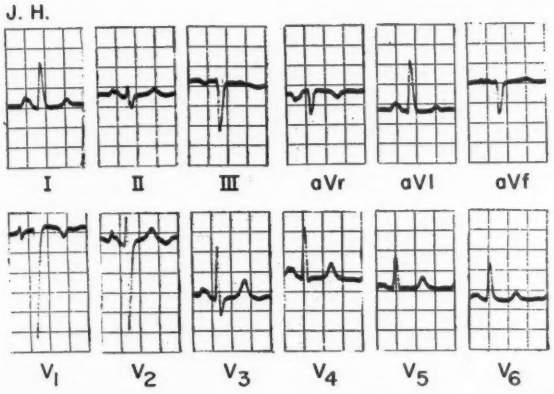


FIG. 4. Electrocardiogram of a 24 year old female with tricuspid atresia. The P waves are broad and notched, a left axis deviation is present, the intraventricular conduction time is slightly prolonged, and the unipolar leads are characteristic of left ventricular preponderance.

The 8 patients with isolated pulmonic stenosis whom we have studied form an especially interesting group. Their ages ranged from 3 to 43 years and the diagnosis was established in each case by cardiac catheterization. No arrhythmias were observed and no auriculoventricular or intraventricular block was seen with the exception of a possible incomplete right bundle branch block in 1 case. The P waves were normal in three tracings and in the remaining five were peaked with slight to moderate increases in amplitude (0.17 to 0.3 millivolt), notably in leads V_1, V_2 and V_3, and less often in the limb leads. The axis was entirely normal (+50°) in one case, a vertical to mild right axis deviation (+90° to +110°) was present in 4 cases, and a high degree of

for the age of the patient. The 5 cases with definite signs of right ventricular hypertrophy in their electrocardiograms (one is illustrated in figure 5) were associated with resting right ventricular systolic pressures of 100 mm. Hg or more; the patient whose electrocardiogram was merely suggestive of right ventricular hypertrophy showed a resting right ventricular systolic pressure of 100 mm. of mercury.

Pulmonic Stenosis and Auricular Septal Defect

The clinical and laboratory features of patients with pulmonic stenosis and auricular septal defect have been well summarized by Selzer and his associates,[18] who comment on the great frequency of prominent tall P waves

and right axis deviation. Engle, Taussig, and Bruins[19] have also recently reviewed this syndrome and have described similar findings

sis was established by autopsy. Their ages ranged from 3 weeks to 28 years. Analysis of the electrocardiograms showed a sinus rhythm

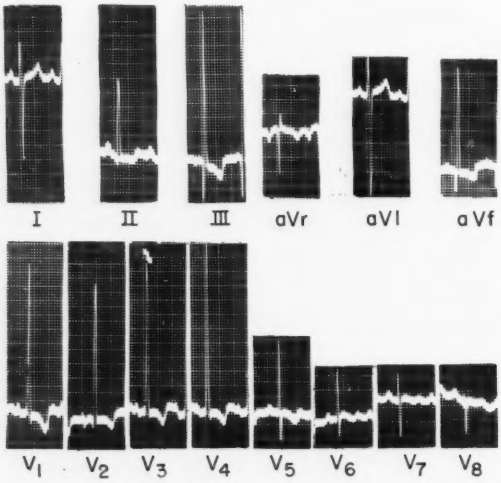


FIG. 5. Electrocardiogram of a 7 year old female with isolated pulmonic stenosis, showing right axis deviation with precordial leads typical of a high degree of right ventricular hypertrophy, very high R waves being present in leads V_1 through V_4.

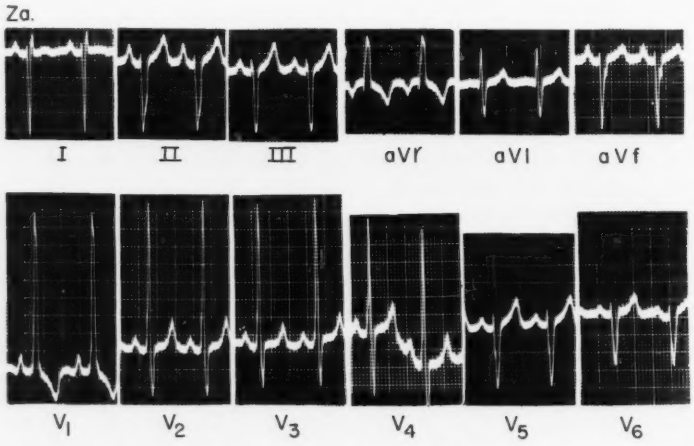


FIG. 6. Electrocardiogram of a 9 year old boy with pulmonic stenosis and auricular septal defect. The P waves are tall, and the precordial leads, as in figure 5, are typical of right ventricular hypertrophy.

including the presence of right bundle branch block or evidences of right ventricular hypertrophy.

In our own series of 7 cases, 5 were studied by cardiac catheterization and in 2 the diagnosis was established by autopsy. Their ages ranged from 3 weeks to 28 years. Analysis of the electrocardiograms showed a sinus rhythm in all, without auriculoventricular or intraventricular block. The P waves were peaked and increased in amplitude in five instances, being most abnormal in leads V_1 through V_4. Right axis deviation (greater than $+115°$) was

seen in all cases, and the voltage was increased in the precordial leads in three of the seven tracings. In addition, the precordial leads were characteristic of right ventricular hypertrophy in four records and suggested it in one other. Figure 6 shows an electrocardiogram of a 9 year old boy with this condition, illustrating the abnormal tall P waves, the high degree of right axis deviation, and the evidences of right ventricular hypertrophy.

The Tetralogy of Fallot

Maude Abbott's *Atlas of Congenital Cardiac Disease*[20] includes the electrocardiograms of 3 patients with the tetralogy of Fallot. All three of these tracings, which were limited to the standard bipolar limb leads, showed a well marked right axis deviation, and high P waves in lead II. In one, a partial variable auriculoventricular block was described. More recently, Taussig[5] has stated that in this condition, the electrocardiogram always shows a "marked right axis deviation and usually the P waves are abnormally high and pointed," and Dry[21] has commented that right axis deviation of moderate to marked degree is "nearly always present," that high and pointed P waves are common, and that conduction disturbances may also occur.

We have studied the electrocardiograms of 15 patients, aged 9 months to 37 years, all of whom were diagnosed by cardiac catheterization, operation, autopsy or combinations of these methods as having the tetralogy of Fallot.* The rhythm was normal in 13 of these, one showed a wandering auricular pacemaker, and one revealed auricular fibrillation (coexisting thyrotoxicosis was suspected clinically). Prominent and typically peaked P waves were seen in 13 tracings, being found chiefly in leads V_{3R}, V_1, V_2 or V_3, and less often in leads II, III, V_4, V_5 and in lead aV_R (where they were sharply inverted). In one electrocardiogram, recorded on an 18 month old patient, the axis was +90°; in another fourteen right axis deviation over +100° was present and in nine, the axis was +120° or more. The voltage appeared high in all but three tracings. Evidences of right ventricular hypertrophy were also suggested by the presence of a high R or R′ in lead aV_R in nine electrocardiograms, and in twelve, the precordial leads showed findings typical of right ventricular hypertrophy with a reversal of the usual R/S ratio (one of the twelve also demon-

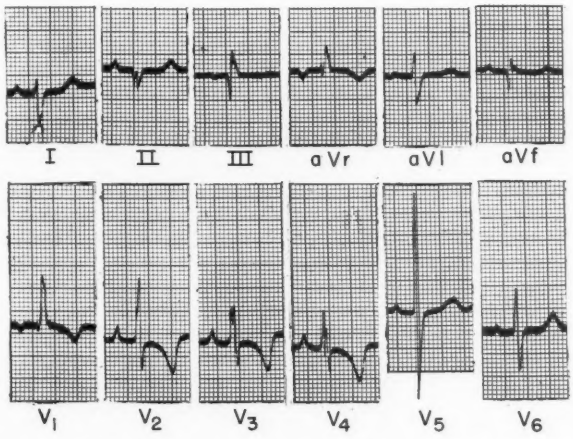


Fig. 7. Electrocardiogram of a 37 year old female with the tetralogy of Fallot. The P waves are peaked in leads V_2, V_3, and V_4, a right axis deviation is present, and the precordial leads show right ventricular preponderance.

* In 1 of these patients, an associated patent ductus was suspected at operation, although not demonstrated by cardiac catheterization, and in another, an associated auricular septal defect was suggested but not proved by cardiac catheterization.

strated a slightly prolonged QRS interval with the right bundle branch block type of QRS, i.e. rsR′ in lead V_1). The precordial leads in one tracing showed RS complexes of similar form in all positions recorded, and in two electrocardiograms a mixed progression was found. RS-T and T wave changes consistent with right ventricular "strain" were seen in only five electrocardiograms.

Figure 7 illustrates the electrocardiogram of a 37 year old woman with this condition, showing peaked P waves in leads V_2, V_3 and V_4, a right axis deviation, and the signs of right ventricular hypertrophy described above. The intraventricular conduction time is slightly prolonged and lead V_1 shows the right bundle branch block pattern.*

Pulmonic Stenosis and Aortic Regurgitation

The combination of pulmonic stenosis and free aortic regurgitation must be rare indeed. By chance, we have had an opportunity to observe and study with data obtained by cardiac catheterization 2 such cases. Both patients were males, aged 16 and 17 respectively, both were known to have heart murmurs recognized in early infancy (one at 3 weeks of age and the other at 4 weeks), and both showed wide pulse pressures without evidence of peripheral arteriovenous fistulas, large hearts, and loud basal systolic and diastolic murmurs. Neither patient gave a history of rheumatic fever or chorea, and it is possible that they represent congenital endocardial sclerosis with valvular deformities.

Their electrocardiograms have certain similarities in that no arrhythmias were observed, the axes were within normal limits, and high voltage QRS complexes were present throughout the precordial leads, which, although indicating left ventricular preponderance, suggested bilateral ventricular hypertrophy by virtue of high voltage, diphasic QRS complexes in leads V_1 and V_2. One tracing in addition reveals broad (0.12 second) P waves and intraventricular block (QRS duration of 0.12 second) without findings characteristic of either right or left bundle branch block.

Transposition of the Great Vessels

The electrocardiographic findings in patients with transposition of the great vessels are said to be usually those of a right ventricular preponderance with large P waves.[22, 23] One case with complete auriculoventricular block has been described.

We have analyzed the tracings of 2 male patients, aged 10 days and 4 months, both studied at autopsy. A sinus rhythm was present with normal P-R and QRS intervals, right axis deviation (+115° and +160°), and peaked P waves which in 1 case were high. Tall R waves were seen in lead aV_R and the precordial leads showed high voltage diphasic QRS complexes and were consistent with a right ventricular preponderance. Figure 8 illustrates the electrocardiogram of the 10 day old baby with this condition.

Aortic and Subaortic Stenosis

The literature does not contain many reproductions of electrocardiograms from patients with congenital aortic or subaortic stenosis. Schnitker[24] reported 1 case with standard limb leads suggesting the presence of left ventricular hypertrophy, and Taussig,[5] and Brown[4] state that left axis deviation may be found.

We have reviewed the electrocardiograms of 4 patients with presumed aortic or subaortic stenosis. These patients, all males and aged from 2 to 28 years, were diagnosed clinically by the following criteria: (1) presence of a loud cardiac murmur known since infancy or childhood (4 months to 7½ years of age); (2) absence of a history of rheumatic fever or chorea; (3) presence of a grade III or IV systolic murmur, loudest in the second right interspace adjacent to the sternal border, and accompanied by a thrill; (4) absence of evidence of other valvular involvement, and (5) lack of cyanosis or clubbing.

* Since writing the above, we have also seen and studied by cardiac catheterization a 5 year old girl with the tetralogy of Fallot plus an auricular septal defect ("pentalogy"). Her electrocardiogram also showed right axis deviation, high pointed P waves, and evidence of a high degree of right ventricular hypertrophy.

The electrocardiograms of our 4 patients are relatively normal. There are no arrhythmias, auriculoventricular or intraventricular block, unusual P waves, or abnormal axis deviation. The precordial leads are consistent with left ventricular preponderance and the voltage is at the upper limit of normal or slightly increased in all four tracings, but in only one electrocardiogram (that of the oldest patient) are the T waves in leads I, aV_L, V_5, and V_6 characteristic of the classic left ventricular hypertrophy or "strain" pattern. From the electrocardiographic point of view, this lesion seems to be well tolerated.

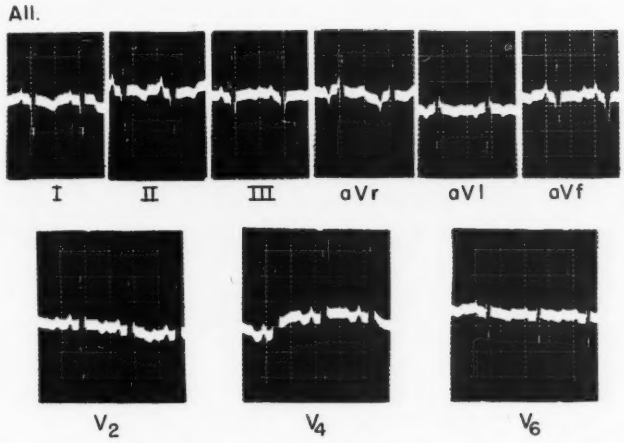


FIG. 8. Electrocardiogram of a 10 day old baby with transposition of the great vessels. The P waves are somewhat peaked, a marked right axis deviation is present, and leads V_2, V_4, and V_6 are consistent with the presence of right ventricular hypertrophy.

COARCTATION OF THE AORTA

Hamilton and Abbott[25] in their comprehensive survey of 200 cases of coarctation of the aorta (1928) commented that in this condition "the electrocardiogram . . . almost invariably shows a left-sided preponderance." In 1942, Rhodes and Durbin[26] summarized the electrocardiographic findings in an additional 116 cases recorded in the literature and observed that 32 of the tracings were normal, 57 showed a left axis deviation, 8 a right axis deviation and 17 revealed prolongation of the intraventricular conduction time; various other findings were listed for 14 of the cases. Of the 8 patients whose tracings were characterized by a right axis deviation, 4 had intraventricular block and three of these were associated with a patent ductus arteriosus, and of the 4 cases without block, 3 lacked pathologic proof of the diagnosis and 1 of these probably also had an associated patent ductus arteriosus. On the basis of their data, it would appear that a right axis deviation is very rare in uncomplicated examples of coarctation of the aorta but that it may occur in association with a patent ductus, presumably by greatly increasing the pressure in the pulmonary artery leading to right ventricular hypertrophy. Stalker[27] has also described a 50 year old female with coarctation whose electrocardiogram showed auricular fibrillation with right axis deviation. Here again, another condition which would explain this axis was present, namely diffuse pulmonary fibrosis. The patient described by Moragues, Moore, and Rossen,[28] also was found to have a tracing with some right axis deviation, but at autopsy the left ventricle was hypertrophied to a greater extent than the right. Unipolar limb leads as well as complete precordial leads might have disclosed evidence of a normal or increased left ventricular preponderance in a vertical type of heart. Christensen and Hines[29] noted that evidence of left ventricular hypertrophy or "strain" was found in one-third of the electrocardio-

grams in a series of 64 patients studied at the Mayo Clinic. Recently, Sokolow and Edgar[30] have referred to the electrocardiographic findings in 24 cases of coarctation of the aorta, observing five normal records, fourteen with evidence of left ventricular hypertrophy, three (with other congenital defects) with right ventricular hypertrophy, and two with right bundle branch block in association with left ventricular hypertrophy.

We have reviewed the electrocardiograms of 8 male and 3 female patients with coarctation of the aorta. Their ages ranged from 8 to 24 years and the diagnosis was proved by aortic catheterization in one and by operation in the remaining 10 cases. The rhythm was normal in all but one tracing, which showed inverted P waves with a normal P-R interval in leads II, III, and aV_F in a vertical heart, evidence of an ectopic auricular pacemaker. Five of the electrocardiograms showed no signs whatever of left ventricular hypertrophy; three others suggested left ventricular hypertrophy (deep S waves in right precordial leads in two and inverted T waves in leads I, V_5 and V_6 in another; see fig. 9). On the whole, no very impressive evidence of left ventricular enlargement was found. One electrocardiogram recorded on a 15 year old male with a blood pressure of 240/120 revealed a typical incomplete right bundle branch block. Two others showed intraventricular conduction times at the upper limit of normal associated with an rSr′ type of QRS complex in leads V_1 and V_2 with persistent S waves in leads V_5 and V_6, also suggesting an incomplete right bundle branch block. There was no precise correlation of electrocardiographic abnormality with age or with blood pressure readings, although the patients with the highest pressures tended to have abnormal tracings.

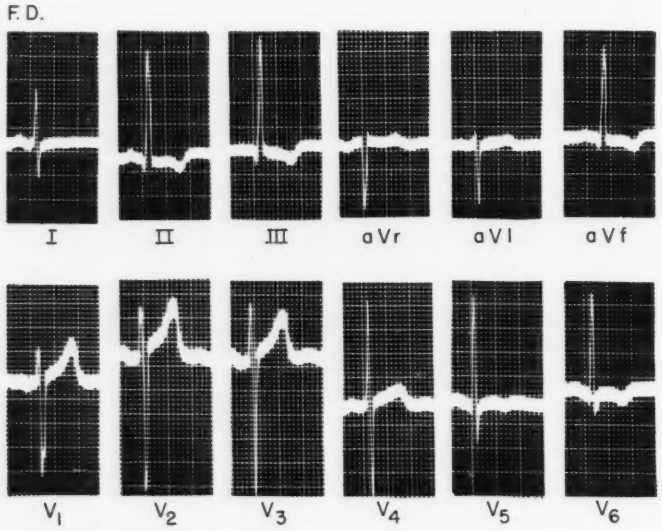


FIG. 9. Electrocardiogram of a 17 year old male with coarctation of the aorta. The tracing is consistent with left ventricular hypertrophy in a vertical heart.

PATENT DUCTUS ARTERIOSUS

It is generally agreed that the electrocardiogram is normal in the vast majority of patients with the diagnosis of uncomplicated patent ductus arteriosus.[4, 5, 31, 32] As is clear from the report of Keys and Shapiro[33] on patency of the ductus arteriosus in adults, hypertrophy of both ventricles eventually occurs and therefore a relative balance is usually maintained with neither an undue right nor an undue left ventricular preponderance pattern appearing (although high voltage QRS complexes may be found). It is of the greatest importance, however, to stress the fact that a mild right

axis deviation is by no means a rarity in this condition. Bullock, Jones and Dooley,[34] Steinberg, Grishman, and Sussman,[35] Shapiro,[31] Benn[36] and many others have reported proved cases whose electrocardiograms showed some degree of right axis deviation. It is in this type of situation that the mistake must not be made of assuming that a right axis deviation is synonymous with right ventricular hypertrophy, and that hence the patient cannot be considered as having an isolated patent ductus arteriosus; adequate study of unipolar limb and chest leads should be made and it will usually be found—as is clear in the data reported below—that there is merely a vertical heart pattern without evidence of a right ventricular preponderance. Exceptionally, a true right ventricular hypertrophy may occur in patients in the older age group in whom a widely patent ductus is found associated with pulmonary arteriolar sclerosis (as reported by both Levine[37] and Ulrich[38]). As to other uncommon findings, Levine and Geremia[32] have described some prolongation of the QRS interval and inversion of the T waves in leads I and II, each occuring twice among 34 cases, and Dry, Harrington, and Edwards[39] have reported a case associated with auricular fibrillation similar to one we have seen.

We have analyzed the electrocardiograms of 24 patients, aged 4 to 36 years, in all of whom the diagnosis of patent ductus arteriosus was confirmed by operation or cardiac catheterization or by both of these methods. Except for frequent ventricular premature beats in one tracing, the rhythm was normal in each case and neither auriculoventricular nor intraventricular block were seen. The P waves were not remarkable in twenty-one records, and were slightly prominent in three others. One electrocardiogram showed a tendency to left axis deviation ($-10°$), two showed a vertical axis, and in one there was a tendency to right axis deviation ($+95°$). The axis was entirely normal in the remainder. It is important to stress the fact that a vertical axis or slight right axis deviation may occur with an uncomplicated ductus arteriosus and, indeed, two tracings had been wrongly interpreted as showing a predominant right ventricle because of this finding. The QRS progression in the precordial leads indicated predominance of the left ventricle in all cases and actual left ventricular hypertrophy was suggested in 6 cases either by the presence of deep S waves in leads V_1, V_2 or V_3 or by high R waves in V_5 or V_6. In addition, three tracings revealed high-voltage diphasic RS complexes over the right, or right and middle precordial leads, with high R waves in leads V_4, V_5 or V_6 sug-

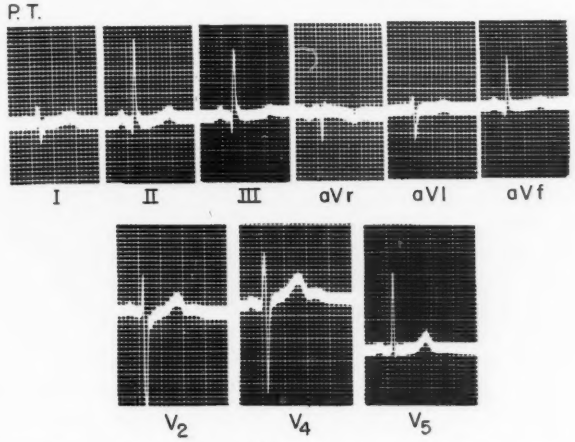


FIG. 10. Electrocardiogram of a 14 year old female with an uncomplicated patent ductus arteriosus, showing the presence of a slight right axis deviation. A normal left ventricular preponderance is seen in the precordial leads.

gesting that combined ventricular hypertrophy existed. The RS-T segments and T waves showed no characteristic changes.

Figure 10 illustrates a slight right axis deviation occurring in the electrocardiogram of a 14 year old patient with an uncomplicated patent ductus arteriosus.

Although it is not included in this series, we wish to mention the electrocardiogram of a 42 year old woman known to have had heart disease since infancy in whom the diagnosis of patent ductus arteriosus had been made at the Massachusetts General Hospital on the basis of characteristic clinical findings with a typical x-ray picture. The diagnosis was confirmed by independent studies at another hospital. The patient declined surgery and permission for autopsy was refused at the time of her death from congestive heart failure, so that final proof as to the anomaly is lacking although there is little doubt as to the nature of the lesion. Her electrocardiograms showed auricular fibrillation associated with a considerable degree of left axis deviation (−30°) with a characteristic left ventricular hypertrophy pattern in the limb and chest leads including a very high R in lead CF_5.

We have not correlated the electrocardiographic findings with the ductus size as estimated at operation. It has been our experience that what appears to be grossly a ductus of large dimensions shunting a great volume of blood may be found to be pathologically associated with a variable and often small aortic or pulmonary arterial opening.

Miscellaneous Cases

We have had an opportunity to observe 1 unusual cyanotic female infant from birth until her death at the age of 6 months. At autopsy, a congenital endocardial sclerosis of the right ventricle was found associated with pulmonic stenosis, slight tricuspid stenosis, and a patent foramen ovale. The right ventricle was thick walled but of small capacity; the left ventricle and right auricle were both hypertrophied. Electrocardiograms on this patient were confusing, initially suggesting left ventricular hypertrophy in a vertical heart, and later indicating a ventricular balance with RS complexes of similar contour in leads V_1 through V_6. The axis was vertical and the P waves were peaked and high.

Another female patient, aged 15 years, was found at autopsy to have a combination of a patent ductus arteriosus plus scarring of the mitral valve and adjacent endocardium (rheumatic?, endocardial sclerotic basis?). Both ventricles were hypertrophied, the left being thicker than the right. Her electrocardiogram showed a sinus rhythm, a vertical axis, normal P-R and QRS intervals, and high voltage R waves in leads aV_F and V_6 with a deep S in V_2 consistent with left ventricular hypertrophy. The T wave in lead V_6 was slightly diphasic.

Finally, we have followed for some years a 9 year old boy, previously reported,[40] who at operation was found to have an arteriovenous fistula between the right coronary artery and the coronary sinus. The electrocardiogram on this patient was within normal limits.

Discussion

Certain general conclusions can be drawn from such a group of electrocardiograms. It is apparent that arrhythmias are not common in patients with congenital heart disease; indeed, they are seen with frequency only in Lutembacher's syndrome in which others have reported a considerable incidence of auricular fibrillation and auricular flutter. The study of P waves has been rewarding, and it has been observed that analysis of the precordial leads, notably V_{3R}, V_1, and V_2, often yielded more information as to unusual size and contour of these waves than did the limb leads which have received so much attention in the past. Abnormal P waves were most often associated with pulmonic stenosis, in which they were characteristically high and peaked. High peaked P waves also have been found in Ebstein's disease, and we have noted broad and high P waves in tricuspid atresia.

It is important to appreciate the value of multiple precordial leads in a determination of relative ventricular preponderance, as compared with axis deviation. This is of course a familiar observation, but it will bear particular repetition in the field of congenital heart disease in which so much emphasis has been

placed on right axis deviation as contrasted with left axis deviation. As pointed out above, axis deviation should be interpreted in the light of findings in unipolar limb and multiple precordial leads, and the presence of a vertical or right axis is not adequate evidence of right ventricular hypertrophy. Where clear signs of right ventricular preponderance are seen electrocardiographically, cardiac catheterization has usually revealed an elevation of the right ventricular systolic pressure above 100 mm. of mercury. It has also been noted that the incomplete right bundle branch block pattern may occur in association with right ventricular hypertrophy, leads aV_R and V_1 quite commonly showing a late R′ with a late S wave in leads V_5 and V_6. RS-T segment and T wave changes of the "strain" type were infrequent, even in the presence of definite unilateral ventricular hypertrophy.

Our series includes only one electrocardiogram with A-V block, recorded on a patient with Eisenmenger's complex. Intraventricular block, usually right, was observed with auricular septal defects, ventricular septal defects, Ebstein's disease, and with coarctation of the aorta.

Summary

1. The electrocardiographic findings encountered in a group of 101 patients with congenital heart disease have been reviewed.

2. Arrhythmias were rare.

3. Abnormal P waves were best seen in leads V_{3R} through V_3 and were most often associated with pulmonic stenosis, complicated or uncomplicated, where they were peaked. They were also found in association with tricuspid valve disease.

4. The most valuable information as to relative ventricular preponderance was obtained from the QRS complexes in multiple chest leads; axis deviation was of lesser importance and at times misleading.

5. Analysis of the RS-T segments and T waves was usually unrewarding; the "strain" pattern was not common, even in the presence of a high degree of unilateral ventricular hypertrophy.

6. Intraventricular block was seen with auricular septal defects, ventricular septal defects, Ebstein's disease, and with coarctation of the aorta.

Acknowledgment

We are grateful to many physicians in both Chicago and Boston who have allowed us to include their patients in this study.

References

[1] McCulloch, H.: Electrocardiographic studies of congenital heart disease. Am. J. Dis. Child. **12:** 30, 1916.

[2] Roesler, H.: Interatrial septal defect. Arch. Int. Med. **54:** 339, 1934.

[3] Bedford, D. Evan, Papp, C., and Parkinson, J.: Atrial septal defect. Brit. Heart J. **3:** 37, 1941.

[4] Brown, J. W.: Congenital Heart Disease. John Bale, London, 1939.

[5] Taussig, H. B.: Congenital Malformations of the Heart. New York, Commonwealth Fund, 1947.

[6] Brannon, E. S., Weens, H. S., and Warren, J. V.: Atrial septal defect: study of hemodynamics by the technique of right heart catheterization. Am. J. M. Sc. **210:** 480, 1945.

[7] Baumgartner, E. A., and Abbott, M. E.: Interventricular septal defect with dextroposition of aorta and dilatation of the pulmonary artery ("Eisenmenger complex") terminating by cerebral abscess. Am. J. M. Sc. **177:** 639, 1929.

[8] Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Physiological studies in congenital heart disease: III. Results obtained in five cases of Eisenmenger's complex. Bull. Johns Hopkins Hosp. **80:** 323, 1947.

[9] Ash, R., Wolman, I. J., and Bromer, R. S.: Diagnosis of congenital cardiac defects in infancy: a study of thirty-two cases with necropsies. Am. J. Dis. Child. **58:** 8, 1939.

[10] Glendy, M. M., Glendy, R. E., and White, P. D.: Cor biatriatum triloculare: case report. Am. Heart J. **28:** 395, 1944.

[11] Yater, W. M., and Shapiro, M. J.: Congenital displacement of the tricuspid valve (Ebstein's disease): review and report of a case with electrocardiographic abnormalities and detailed histologic study of the conduction system. Ann. Int. Med. **11:** 1043, 1937.

[12] Engle, M. E., Payne, T. P. B., Bruins, C., and Taussig, H. B.: Ebstein's anomaly of the tricuspid valve. Report of three cases and analysis of clinical syndrome. Circulation **1:** 1246, 1950.

[13] Blackford, L. M., and Hoppe, L. D.: Functionally two chambered heart. Am. J. Dis. Child. **41:** 1111, 1931.

[14] Taussig, H. B.: Clinical and pathological findings in congenital malformations of the heart due to

defective development of the right ventricle associated with tricuspid atresia or hypoplasia. Bull. Johns Hopkins Hosp. **59:** 435, 1936.

[15] Currens, J. H., Kinney, T. D., and White, P. D.: Pulmonary stenosis with intact interventricular septum. Am. Heart J. **30:** 491, 1945.

[16] Greene, D. G., Baldwin, E. de F., Baldwin, J. S., Himmelstein, A., Roh, C. E., and Cournand, A.: Pure congenital pulmonary stenosis and idiopathic congenital dilatation of the pulmonary artery. Am. J. Med. **6:** 24, 1949.

[17] Blackford, L. M., and Parker, F. P.: Pulmonary stenosis with bundle branch block: report of a case with sound tracings and semiserial studies of the conduction system. Arch. Int. Med. **67:** 1107, 1941.

[18] Selzer, A., Carnes, W. H., Noble, C. A., Jr., Higgins, W. H., Jr., and Holmes, R. O.: The syndrome of pulmonary stenosis with patent foramen ovale. Am. J. Med. **6:** 3, 1949.

[19] Engle, M. A., Taussig, H. B., and Bruins, C.: The clinical syndrome produced by valvular pulmonic stenosis with intact ventricular septum and patent foramen ovale. Program, Twenty-Third Annual Scientific Sessions, Am. Heart Assoc., June 22–24, 1950, p. 27.

[20] Abbott, M. E.: Atlas of Congenital Cardiac Disease. New York, American Heart Association, 1936.

[21] Dry, T. J.: Classic clinical features of tetralogy of Fallot. Proc. Staff Meet., Mayo Clin. **22:** 173, 1947.

[22] Taussig, H. B.: Complete transposition of the great vessels. Am. Heart J. **16:** 728, 1938.

[23] Ingham, D. W., and Willius, F. A.: Congenital transposition of the great arterial trunks. Am. Heart J. **15:** 482, 1938.

[24] Schnitker, M. A.: The electrocardiogram in congenital cardiac disease: a study of one hundred and nine cases, one hundred and six with autopsy. Cambridge, Mass., Harvard Univ. Press, 1940.

[25] Hamilton, W. F., and Abbott, M. E.: Coarctation of aorta of adult type; complete obliteration of descending arch at insertion of ductus in boy of fourteen; bicuspid aortic valve; impending rupture of aorta; cerebral death; statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of descending arch in subjects above age of two years. Am. Heart J. **3:** 381, 1928.

[26] Rhodes, P. H., and Durbin, E.: Coarctation of the aorta in childhood: review of the literature and report of three cases. Am. J. Dis. Child. **64:** 1073, 1942.

[27] Stalker, H.: Coarctation of the aorta: a case with right axis deviation of the electrocardiogram and auricular fibrillation with some statistics. J. Michigan M. Soc. **41:** 40, 1942.

[28] Moragues, V., Moore, L. T., and Rossen, J. A.: Coarctation of the aorta, with rupture of the wall below the point of constriction. Am. Heart J. **24:** 828, 1942.

[29] Christensen, N. A., and Hines, E. A., Jr.: Clinical features in coarctation of the aorta: a review of ninety-six cases. Proc. Staff Meet., Mayo Clin. **23:** 339, 1948.

[30] Sokolow, M., and Edgar, A. L.: A study of unipolar precordial and limb lead electrocardiograms in congenital heart disease. Am. J. Med. **8:** 528, 1950.

[31] Shapiro, M. J.: The preoperative diagnosis of patent ductus arteriosus. J. A. M. A. **15:** 934, 1944.

[32] Levine, S. A., and Geremia, A. E.: Clinical features of patent ductus arteriosus with special reference to cardiac murmurs. Am. J. M. Sc. **213:** 385, 1947.

[33] Keyes, A., and Shapiro, M. J.: Patency of the ductus arteriosus in adults. Am. Heart J. **25:** 158, 1943.

[4] Bullock, L. T., Jones, J. C., and Dolley, F. S.: The diagnosis and the effects of ligation of the patent ductus arteriosus: a report of eleven cases. J. Pediat. **15:** 786, 1939.

[35] Steinberg, M. F., Grishman, A., and Sussman, M. L.: Angiocardiography in congenital heart disease. III. Patent ductus arteriosus. Am. J. Roentgenol. **50:** 306, 1943.

[36] Benn, J.: The prognosis of patent ductus arteriosus. Brit. Heart J. **9:** 283, 1947.

[37] Levine, S. A.: The diagnosis of patent ductus arteriosus and the indications for operation. Acta med. Scand., Suppl. 196. **128:** 145, 1947.

[38] Ulrich, H. L.: Report of a case of patent ductus arteriosus with some unusual features. Acta med. Scand., Suppl. 196. **128:** 160, 1947.

[39] Dry, T. J., Harrington, S. W., and Edwards, J. E.: Irreversible cardiac disease in adult life caused by delayed closure of a patent ductus arteriosus. Report of case. Proc. Staff Meet., Mayo Clin. **23:** 267, 1948.

[40] Paul, O., Sweet, R. H., and White, P. D.: Coronary arteriovenous fistula. Am. Heart J. **37:** 441, 1949.

Vibrations of Low Frequency over the Precordium

By Franklin D. Johnston, M.D., and Donald C. Overy, M.D.

A method for taking tracings which represent actual movements of the precordium (displacement curves) or records which show waves proportional to the velocity of movement of the chest wall (velocity curves) is described. The equipment employed is readily available, and the method is easy to use. The displacement curves are nearly identical with cardiograms taken with a good optical setup, and they may have diagnostic value. The velocity curves are more closely related to the functional status of the myocardium. The clinical significance of these tracings, especially the former, is pointed out.

VIBRATIONS of many different kinds are produced by mechanical activity of the heart, and these may be transmitted through the chest wall and be detected by inspection, palpation, auscultation or by more elaborate instrumental methods. The heart sounds, murmurs and other auscultatory findings heard with the stethoscope are due to vibrations within the audible range (average frequency, 20 to 30 cycles per second or more), and much information relative to structural defects or functional disorders of the heart is, of course, obtained from these phenomena. Few physicians realize that these audible vibrations are usually insignificant in amplitude compared with those of low frequency. The latter may be seen and felt, but they are not heard on auscultation, and comparatively little attention has been paid to them. It is true that the apex beat or point of maximal impulse (PMI) is often referred to in a cursory fashion, but rarely is the character of the low frequency pulsations that cause it studied in any detail, and vibrations that may be seen or felt elsewhere over the precordium are often completely neglected.

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich. This study was made possible by a grant to Dr. Frank N. Wilson from the S. S. Kresge Foundation. This material was presented in condensed form at The Twenty-third Scientific Session of the American Heart Association in San Francisco, California, on June 23, 1950.

Dr. Overy is working in the Heart Station as Research Assistant on funds supplied by the Michigan Heart Association.

Instruments for recording vibrations over the precordium have been available for many years in the form of tambours connected with levers arranged to write on smoked paper, and records (apex cardiograms) taken with such equipment may still be found in some text books of physiology. The poor frequency response and great mechanical lag inherent in such apparatus make these tracings nearly valueless, but optical methods developed by Frank,[1] Frank and Hess,[2] and refined by Wiggers[3] make it possible to record vibrations occurring over the precordium or elsewhere with a high degree of accuracy. Weitz,[4] using the optical method of Frank with a somewhat different pickup device, recorded vibrations from the cardiac apex in normal subjects and in patients with different types of heart diesase and claimed that alterations in the tracings characteristic of cardiac enlargement and of various types of valve lesions were present. Crehore,[5, 6] using an ingenious optical method employing interference bands, recorded the apex beat in a number of subjects and concluded that these records should "be of use not only for research work but also for clinical purposes."

Suggestions that apex cardiograms may represent a record of intraventricular pressures have been denied by Wiggers,[7] who states that "the apex beat represents only the varying pressure of the cardiac apex on the thoracic tissue; and this is solely governed by the shifting of the heart's position and its degree of filling." In the last edition of his book, *Circulation in Health and Disease*, Wiggers[7]

implies but does not clearly state that apex cardiograms, even those taken with adequate technics, are not likely to be of much clinical value. One wonders if this pronouncement may not have discouraged further work in this field. In 1933 Dressler published a book on the pulsations of the chest wall[8] in which basic anatomic considerations, experimental studies on animals and a vast clinical experience were woven together to produce a volume of incomparable value to any physician interested in precordial vibrations of low frequency. It is unfortunate that much of the material in this book is unknown to most physicians, since careful inspection and palpation, guided by interest and experience, will, as Dressler points out, help tremendously in the diagnosis of many heart lesions.

Kountz, Smith, Gilson and co-workers have published several papers[9-12] within the last 10 years relating to the use of the cathode ray oscillograph and associated equipment for the study of the heart sounds and vibrations in the subaudible range appearing over the precordium. Many interesting and important matters are brought out in these papers, but the work might be critized because the frequency response of the apparatus was not adequate to record vibrations having a frequency much below 5 cycles per second. Furthermore, the dynamic microphone employed gave tracings which record the velocity of movement of the precordium and not its displacement, and these records are not, therefore, comparable to cardiograms taken with optical methods, since the latter are usually true displacement curves.

In an excellent discussion, *The Graphic Registration of the Normal Heart Sounds*, Rappaport and Sprague[13] clearly point out problems involved in the registration of audible vibrations as well as those below the audible range and emphasize that the amplitude of the latter may be very much greater than the former. Using a crystal microphone for recording the pulse wave, described by Miller and White,[14] Rappaport and Sprague have taken tracings, which they call "linear" phonocardiograms, in which vibrations of low frequency dominate. These records probably represent with fair accuracy displacements of the chest wall beneath the pickup employed and, if the microphone arrangement were suitably coupled to a direct current amplifier, tracings closely resembling those obtained with a well designed optical setup should be recorded. It should be pointed out that the equipment under discussion was not designed to record static pressure changes within the tubing leading to the crystal, and its response to slow displacements of the chest wall might not be very accurate.

Foulger and associates[15-17] have studied precordial vibrations of subaudible frequencies in man and several species of animals primarily from the standpoint of the changes in their intensity or frequency, or both, induced by various physiologic variables (such as exercise) or by toxic agents. In a subject with a normal heart, exercise increases the average frequency of vibrations in the subaudible range, and anoxia or other deleterious agents lowers these frequencies. These frequencies are below the usual normal range in most patients with serious heart disease in the resting state, and effects of exercise in such individuals suggests that estimation of the low frequency spectrum may give important information about the functional capacity of the myocardium.

Mannheimer[18] has recorded precordial vibrations over a wide range of frequencies by using multiple amplifiers and recorders, and more recently Dunn and Rahm[19] have carried out studies along similar lines. The latter emphasized the complexity of the waves that represent vibrations arising in the heart, the great amplitude of low frequency vibrations as compared with those in the audible range, and pointed out that visual study of records, taken with full knowledge and appreciation of the frequency response of the equipment employed, is of basic importance in work of this kind. They mention the importance of some sort of method for analyzing these records of vibrations and discuss some of the difficulties involved. Burger and Koopman[20] have made mathematical analyses of vibration records from normal subjects, thus obtaining data which give the approximate frequency spectrum of the heart sounds in the subaudible as well as in the higher frequency

range. These studies are similar in some respects to those carried out by Foulger and associates.

It is clear that many workers have been interested in vibrations of low frequency over the precordium, but there has been little continuity between the various studies and not a great deal of clinical value has come from them. This somewhat surprising situation is understandable if one remembers that the registration of the vibrations in question has involved the use of more or less complicated apparatus not usually readily available for clinical use, that the proper use of such equipment demands special training and experience, and finally, that different investigators have been interested in and have recorded tracings representing these phenomena for different reasons. Thus, Foulger and his associates have developed methods and apparatus primarily to estimate the range of frequencies that are most prominent in subjects of different types under varying conditions, while the majority of others have been more concerned with the form of vibration records and what they may mean in terms of normal or abnormal structure or function of the heart. Both of these approaches may be important, but for somewhat different reasons.

It is the purpose of this paper to describe a method for the accurate registration of vibrations in the subaudible range using equipment that is readily available and simple to use. Several records taken on subjects with normal hearts and different types of heart disease are presented, and the possible value of the tracings in this relatively unexplored field is discussed.

Method

An instrument designed primarily for studies in a somewhat different field has been found to perform very well as the basic unit in a setup to record vibrations of low frequency over the precordium. This is the electromanometer designed and built by the Sanborn Company of Cambridge, Massachusetts. Since this device employs an oscillating circuit with a balanced bridge arrangement having a transducer of capacity type in one arm of the bridge, its output is proportional to pressures transmitted to one plate of the condenser from any desired external source. If the system of tubing leading to the transducer does not leak, the instrument will measure constant as well as variable pressures. In other words, if the tube connected to the transducer is attached to a small endpiece resting snugly on the precordium, vibrations of the chest wall, including those of the lowest frequencies, will be faithfully registered by a suitable recording device connected to the output of the electromanometer. The manometer usually supplied for measurement of arterial or venous pressures is not sensitive enough for the purpose at hand, but a more sensitive transducer may be obtained which will avoid this difficulty.

A simultaneous electrocardiogram is very helpful in timing, and we have found it convenient to use a

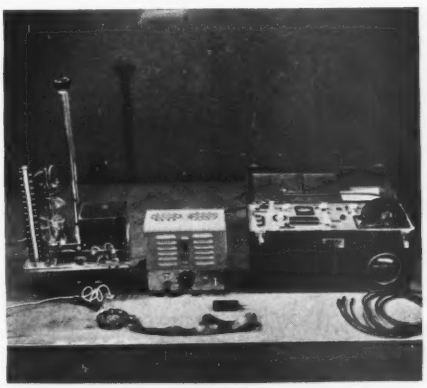


Fig. 1. View of all equipment used to take vibration records. The Sanborn Electromanometer is at the left, and the Tri-Beam Electrocardiograph we have used to record the tracings with a simultaneous electrocardiogram is on the right. The yoke arrangement supporting the endpiece which rests on the chest wall is shown in front of the manometer.

Sanborn Tri-Beam electrocardiograph to record the vibration record and the accompanying electrocardiogram. Figure 1 shows all of the equipment used to take the tracings.

In preliminary tests the tubing attached to the transducer was filled with distilled water, but this makes the entire system very sensitive to external vibrations, and fluid conduction was soon given up and air conduction employed exclusively. Tests have been carried out by means of suitable electric and acoustic circuits which show that a pressure change produced at the endpiece is transmitted to the transducer with a delay of approximately 0.005 second. This lag between acoustic and electrical records is too small to be important, at least for any studies we are doing at the present time. Air conduction probably causes some attenuation of pressure changes of high frequency, but again this is unimportant, since vibrations in the audible range are not primarily under investigation.

A few additional words must be said about the

endpiece and the manner in which it is secured to the precordium. A medium sized endpiece of the Bowles type with the diaphragm removed has been used exclusively. This must be supported so that it *rests firmly on the chest wall and makes an airtight connection*. This is essential, since leakage anywhere in the air space between the transducer and the endpiece will seriously disturb the response at low frequencies. To accomplish this, the endpiece is held by a support attached to a circular lead yoke, which is, in turn, fastened at the desired place on the chest by rubber straps placed around the thorax. (See fig. 2.) The lead yoke is covered with leather, but it can be bent in any desired fashion so that the endpiece will rest squarely and snugly on the chest wall.

FIG. 2. Close-up view of the circular lead yoke which holds the endpiece. See text.

It must be noted that this method of supporting the endpiece is advantageous, since the effects of respiratory movements are minimized, and it gives records which represent vibrations occurring in rather sharply circumscribed areas. It should be mentioned, however, that, if the entire precordium moves with the motion of the underlying heart, the yoke as a whole will also move, and the record obtained may not be a very true picture of actual displacements beneath the endpiece. Studies with other types of equipment, that cannot be described here, make it clear that vibrations closely resembling ballistocardiograms exist, not only over the precordium but over the entire chest, and one reason for the use of the device described above is to minimize these transverse ballistic effects.

It should be clear from the foregoing that the tracings obtained depict outward or inward movements of the chest wall beneath the endpiece and are true displacement curves. They should closely resemble cardiograms taken with a properly arranged optical setup. In our tracings, an upward deflection represents an outward movement of the chest wall beneath the endpiece. For reasons that will be discussed later, it is desirable to record tracings that reflect the velocity of movements of the chest wall as well as the actual displacements, and this is easily accomplished by the use of a differentiating circuit supplied by the Sanborn Company. When this circuit is plugged in, a velocity curve rather than the displacement curve is recorded. Both types of tracings have been taken in all subjects we have studied.

Respiratory movements, by altering the location of the heart with respect to the chest wall, and for other reasons, alter the form of the vibration records considerably. This is particularly true of the displacement curves, and for this reason all of these were taken during suspended respiration. This practice was not generally followed when velocity curves were being taken and explains some of the variations between complexes seen in our records.

RESULTS AND DISCUSSION

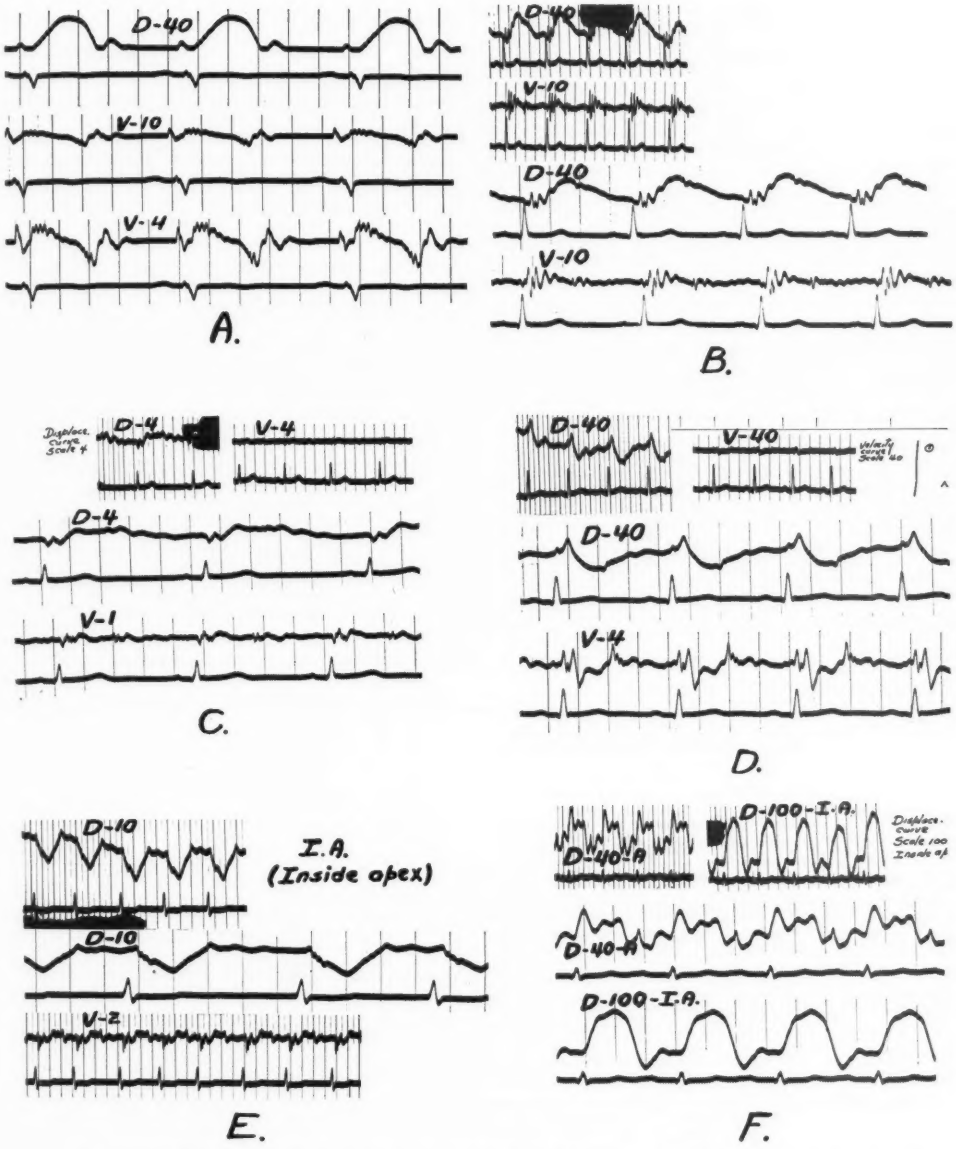
Figures 3 and 4 are reproductions of records taken on different subjects. In all of them the vibration record is above and the electrocardiogram below. The former is labelled to indicate whether it is a displacement or velocity curve, and the sensitivity (scale setting on the electromanometer) used is also given. In many cases records were taken at two different speeds of the recording paper; 25 and 75 mm. per second. All tracings were taken at

FIGURE 3. See facing page.

FIG. 3*A*. Vibration records and simultaneous electrocardiogram (lead II) taken at the apex with the patient lying partially on his left side. The subject here was a man of 67 years with arteriosclerotic heart disease with no cardiac enlargement or signs of congestive failure. Moderate dyspnea on exertion was his only symptom. The heart sounds were faint, and barely audible extra sounds in early and late diastole were present. In these records and in the rest of those seen in figures 3 and 4, the vibration curves are labeled to indicate whether they are displacement or velocity curves, and the sensitivity at which they were taken (scale setting on the electromanometer) is given. Thus D-40 means displacement curve taken at sensitivity of scale 40 and V-10 means velocity curve taken at four times the sensitivity, i.e. scale 10. All records were taken at the apex unless labeled otherwise.

B. Records taken on an 18 year old male with a normal heart. The apex beat was not visible and barely palpable. The heart sounds were somewhat faint, and an inconstant third heart sound was heard. Lead II simultaneously.

C. Records taken on a 28 year old male physician with a normal heart. This individual had a thick chest wall, and no apex beat was visible or palpable. Heart sounds normal. Lead I simultaneously



D. Records taken on a 23 year old male medical student with a normal heart. Lead II simultaneously.

E. Records taken from a point inside the apex on a 44 year old man with constrictive pericarditis. A diastolic heave was present over much of the precordium, and a distinct sound in early diastole was audible at both apex and base. Auricular fibrillation was present. Lead I simultaneously.

F. Records taken at the apex (*A*) and at a point near the left sternal edge at a higher level (*I.A.*) on a 47 year old man with rheumatic heart disease. Mitral and tricuspid lesions were present. Marked systolic pulses in the neck veins and persistence of peripheral edema and hepatomegaly in spite of treatment made the diagnosis of tricuspid disease quite certain here. Lead I simultaneously.

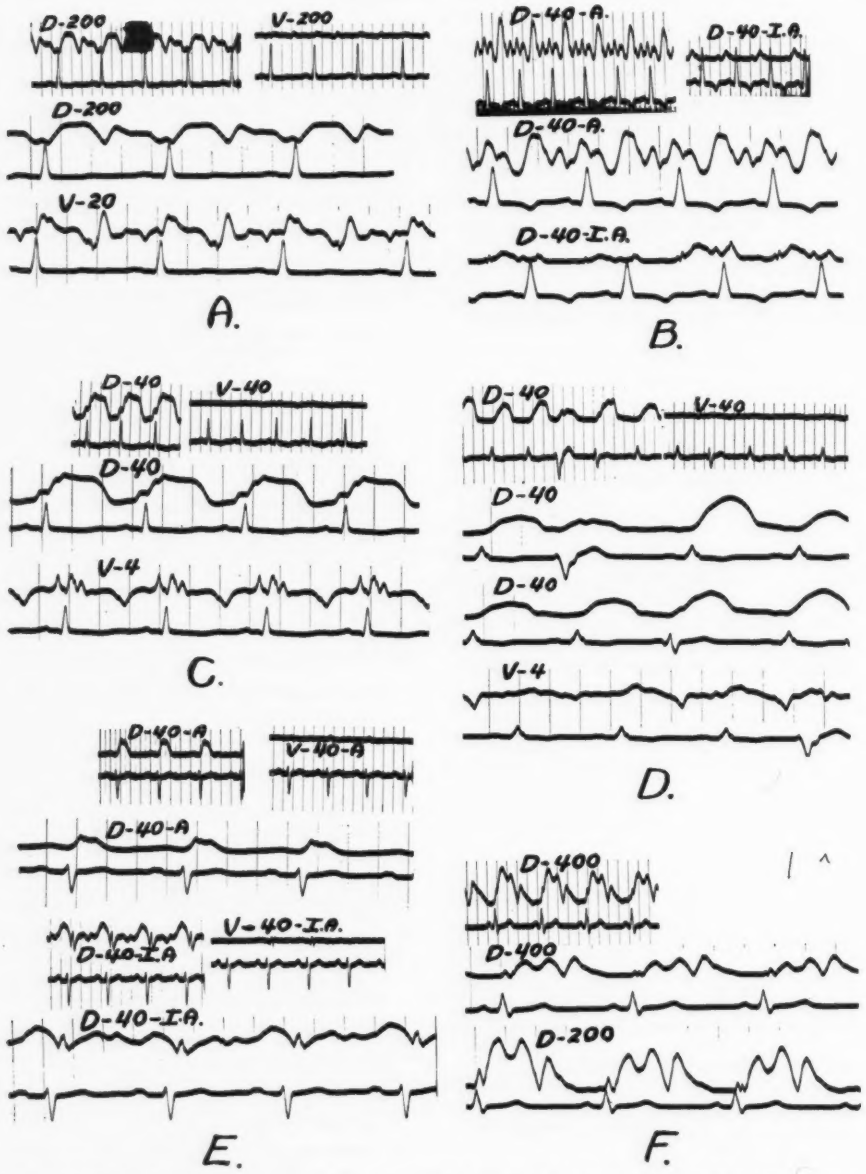


FIG. 4A. Records taken on a man of 38 years with hypertensive heart disease. The heart was enlarged and a double impulse was easily felt at the apex. The first sound at the apex was very faint, and extra sounds in both early and late diastole were audible. It is clear from the displacement curves that the second component of the double apex impulse that could be felt was due to a prominent outthrust in early diastole. Lead I simultaneously.

B. Records taken on a 34 year old man with chronic nephritis and hypertension. Cardiac enlargement was present. Although the displacement curves taken at the apex show large waves of low frequency in both early and late diastole, only an extra sound in presystole was heard. Lead I simultaneously.

C. Records taken on a 63 year old man about two months after anterior myocardial infarction.

the apex unless otherwise noted. A brief statement about the subjects from which each of these records were taken, including important physical findings, is included in the legends describing the figures. This material will not be repeated in the text, except in a few instances, in order that important points may be emphasized.

Because of the simple form of the displacement curve, the tracings shown in figure 3*A* were selected for discussion first. The records in this figure were obtained from a man of 67 years with arteriosclerotic heart disease. At the time they were taken no cardiac enlargement or signs of congestive failure were present, but careful auscultation at the apex with the patient on his left side revealed faint extra sounds in early and late diastole and indistinct heart sounds. Within six months he suffered a serious cardiac breakdown requiring vigorous treatment. The displacement curve consists primarily of three upward waves (representing out-thrusts of the chest wall). Small waves are seen in presystole and early diastole, and a larger one with a rather gradual ascent and more abrupt descent occupies systole. Except possibly for the wave in presystole, the three major waves here are of too low frequency to be audible, and they completely dominate the record. Vibrations corresponding to the first and second sounds are present on the ascending and descending limbs of the major wave in systole, but they appear as scarcely visible ripples or undulations.

The middle and lower sets of tracings in this figure show velocity curves taken from the same point on the precordium (apex) at four and ten times the sensitivity of the displacement curve. As one would expect, these records show vibrations corresponding to the easily audible components (first and second sounds) quite clearly. Since a differentiating circuit was employed to obtain the velocity curve, it must be the derivative of the displacement record. Inspection, in this instance where the vibration records are of relatively simple form, shows that this is true.

It is clear that in the displacement curve taken from this patient with serious myocardial disease, vibrations in the subaudible range are dominant. This appears to be generally true. (See figs. 4*A*, *B*, *C*, *D*). It may be of importance that this tracing showed the characteristics mentioned some months before heart failure appeared and when there were few clinical findings pointing to serious heart disease. Of considerable interest is the fact that low frequency vibrations corresponding in time to barely audible early and late diastolic extra sounds are clearly seen in both displacement and velocity curves. It is well known by anyone experienced in the technic of taking ordinary phonocardiograms that low pitched sounds like diastolic gallop or third heart sounds may be easily recorded even though they are scarcely audible. It appears that these phenomena are due to events which produce vibrations primarily in the subaudible range, since, in our experience and that of others, prominent vibrations of low frequency are regularly found to occur in early or late diastole

---

The heart was of borderline size, and a distinct extra sound in presystole was audible at the apex. Lead I simultaneously.

D. Records taken on a man of 61 years with arteriosclerotic and rheumatic heart disease. The heart was enlarged, the heart sounds were faint and an inconstant early diastolic extra sound was present. Early congestive failure was present at the time this record was taken, and he died a few weeks later. Lead I simultaneously.

E. Displacement curves taken on a 31 year old woman with high grade mitral stenosis, both from the apex (*A*) and from a site along the left sternal edge at a higher level (*I.A.*). Note the prominent upward vibration in presystole seen in the tracing taken in the latter location. Lead I simultaneously.

F. Displacement curves taken on a man of 22 years with aortic insufficiency of rheumatic origin. These records show that a very large systolic out-thrust followed by one in early diastole of nearly equal size was present, since they were taken at low sensitivities. Variation between the relative size of the systolic and early diastolic waves in different records is probably due to the fact that they were taken at different periods of the respiratory cycle. Lead I simultaneously.

in subjects in whom these extra sounds in diastole are heard. (See figs. 4*A*, *B* and *C*) Low frequency vibrations in diastole lacking in higher frequency components and therefore entirely inaudible are often seen in curves taken on normal subjects. These vibrations with or without audible components may appear in exaggerated form in tracings obtained from patients with serious myocardial disease, and a study of them should help to make clear some of the factors responsible for diastolic gallop rhythms.

The tracings taken on normal subjects shown in figures 3*B*, *C* and *D* vary widely in appearance but also have several things in common. While vibrations of very low frequencies are prominent in the displacement curves, oscillations corresponding to at least the major waves of the heart sounds are easily seen, and the velocity curves are not unlike ordinary sound tracings. Small vibrations in early or late diastole are seen in these normal records, and our experience so far indicates that generally speaking the subaudible vibrations both in systole and diastole are smaller compared with oscillations of higher frequency than is true in records from patients with serious myocardial disease. If this is correct, one would expect the velocity curves in patients in the latter group to be relatively smaller, compared to the displacement curves, than is the case in normal subjects. We have the impression that this is true, but further data and a satisfactory method of comparing the amplitudes of displacement and velocity curves will be needed before a positive statement on this matter can be made. It should be mentioned, however, that these concepts are in complete agreement with the ideas of Foulger and co-workers.[15]

Referring again to figures 3*B*, *C* and *D*, it is obvious that the apex impulse is not a simple out-thrust lasting throughout systole in all normal subjects. While this is roughly true in the individuals from whom the first two sets of records were obtained, figure 3*D* makes it clear that, except for a quick outward movement in early systole, the opposite was true in the third normal subject. These variations, even in normal subjects, may be understood if one remembers the previously quoted statement by Wiggers[7] that "the apex beat represents only the varying pressure of the cardiac apex on the thoracic tissue; and this is solely governed by the shifting of the heart's position and its degree of filling." This explanation applies to vibrations of low frequency due to cardiac activity appearing at any point on the precordium and not to apex cardiograms alone. With this in mind, one realizes how many factors existing in the normal subjects, such as basic orientation of the heart with respect to the chest wall and effects of respiration and body position on this relationship, enter to make these vibrations vary tremendously in this group. Dressler[8] points out many of the factors that may produce systolic out-thrusts or the reverse in subjects with normal hearts.

With full realization that relatively little is known about these vibration records even in patients without heart disease, it seems worth while to present a few examples of tracings taken on patients who have structural diseases which alter in a qualitative fashion the filling of the heart as a whole or lead to striking changes in the systolic or diastolic pulsations originating in one or more of its chambers. Thus, in figure 3*E*, vibration records taken from a patient with constrictive pericarditis are reproduced. In this patient a distinct out-thrust in diastole was visible over much of the precordium, and a fairly loud extra sound in early diastole was audible over this entire region. The displacement curves indicate the presence of an outward movement in diastole, and these waves have peculiar flat tops distinctly different from those obtained from any other subject to date. The significance of these flat topped waves becomes clear if one remembers that dense fibrous tissue surrounding the heart will prevent filling and dilatation of the ventricles beyond a certain point in diastole after which these chambers will remain engorged and relatively immobile. Electrokymograms taken on patients with constrictive pericarditis have recently been reported by McKusick[21] to show diastolic waves of very similar outline.

The displacement curves shown in figure 3*F*

were taken from a patient with rheumatic heart disease and insufficiency and stenosis of both mitral and tricuspid valves. One of these records was taken at the apex and the second close to the left sternal edge at a higher level. Both of these tracings show upward waves in presystole and more prominent upward waves in systole. Of considerable interest is the fact that these records show a much greater systolic outpulse in the region near the sternum (probably close to the right auricle) than at the apex. Such a finding would be expected with tricuspid insufficiency but may also be due to right ventricular hypertrophy. Records taken near the sternum in a number of patients with uncomplicated mitral lesions (with normal sinus rhythm) all show large upward vibrations of very low frequency in presystole but in none are very large upward waves in systole (as seen in fig. 3*F*) seen. This is indirect evidence that marked systolic distension of a large right auricle due to tricuspid insufficiency is the cause for the large waves in systole under discussion.

Figure 4*E* shows displacement curves from a patient with high grade mitral stenosis taken at the apex and from a point close to the left sternal edge at a higher level. The latter show the large upward wave in presystole, referred to above. It seems likely that these waves arise from outward pressure of an enlarged and dilated right ventricle during auricular systole. They have been inconspicuous or entirely absent in a few patients with mitral stenosis who have had auricular fibrillation.

The displacement curves shown in figure 4*F* were taken from the apex in a young patient with aortic insufficiency of rheumatic etiology. They were recorded using one-fifth to one-tenth of the sensitivity employed during the registration of most of the records shown in figures 3 and 4, and the upward deflections in systole therefore correspond to a very large systolic out-thrust at the apex. The major bifid wave in systole is followed by a prominent upward wave in early diastole. It is unlikely that this marked out-thrust in early diastole is related to diastolic filling in the usual sense; it is probably due to pressure of the apex against the chest wall caused by blood flowing back into the left ventricle through the incompetent aortic valve. Similar waves of varying sizes have been present in most patients with aortic insufficiency that we have studied.

It seems possible for reasons outlined above that tracings depicting the vibrations of low frequency at certain areas over the precordium may have some value in diagnosis. The displacement curves seem to offer most promise from this standpoint. We do not wish to give an overenthusiastic impression of the value of the method we have described or to leave anyone with the idea that the recording of displacement curves or attempts to explain their possible value is a new concept. Weitz[4] in 1917, using the optical setup mentioned earlier, obtained displacement curves that are strikingly similar to ones we have obtained both in normal and abnormal subjects, and in Dressler's book[8] one will find not only graphic records illustrating pulsations of many different kinds occurring over the precordium but proof that many of these vibrations in the subaudible range may be detected by the physician who is aware of their existence and will look and feel for them. It seems to the writers that many physicians have forgotten the existence of pulsations over the heart that are often visible and palpable but are not audible, and the important role these vibrations should play in the physical examination of the heart. If this paper contributes anything worth while, it may be to recall and to emphasize the importance of earlier work in this field.

Relatively little has been said about the velocity curves and their possible value. Since these records represent the velocity with which pulsations occur (not the actual magnitude or size as is true of displacement curves), one would expect that they may be closely related to the functional status of the myocardium. Thus, in a patient with congestive failure, we may see and feel (and record) large movements over the heart but receive a very definite impression that these phenomena are occurring more slowly than when failure is absent. Evidence derived from displacement curves supporting this view has been mentioned earlier, and we are quite sure, on the basis of work to

date, that velocity curves are small in patients with serious myocardial disease and impaired cardiac function as compared with those from similar subjects in whom function is normal. It seems rather unlikely now that velocity curves will be widely used as a method for estimating the functional status of the heart, but further experience with them and development of technics for using them in a more quantitative fashion may indicate that they are helpful in this field.

Summary

1. Apparatus is described with which accurate registration of vibrations of low frequency existing over the precordium (or elsewhere on the body) is easily accomplished.

2. The method is superior to most of those employed in recent years because it employs a basic unit capable of measuring static pressures. Tracings representing actual pulsations over the precordium (displacement curves) are therefore accurate for vibrations of the lowest frequencies.

3. Tracings showing waves proportional to velocity of movement of the chest wall (velocity curves) may be easily recorded by the use of a differentiating circuit.

4. The velocity curves are related to the functional status of the myocardium and may prove to be of value in this connection.

5. The displacement curves are practically identical with cardiograms taken with a properly arranged optical setup and may show qualitative changes, when taken over certain areas of the precordium in cardiac patients, that have diagnostic value.

6. These vibration records, especially the displacement curves, are important clinically, since they represent displacements of the chest wall that may be quite inaudible and yet are often visible or palpable.

REFERENCES

[1] Frank, O.: Die Herztonkaspel. Ztschr. f. Biol. **50:** 341, 1908.

[2] —, and Hess, O.: Über das Cardiogram und den ersten Herzton. Verhandl. d. Kong. f. inn. Med. **25:** 285, 1908.

[3] Wiggers, C. J.: An adaptation of Frank's segment capsules for clinical use. J. A. M. A. **64:** 1305, 1915.

[4] Weitz, W.: Über die Kardiographie am gesunden Herz mit dem Frank'schen Apparat. Über die Kardiographie des pathologischen Herzens mit dem Frank'schen Apparat. Deutsch. Arch. f. klin. Med. **124:** 134, 155, 1917.

[5] Crehore, A. C., and Meara, F. S.: The micrograph. J. Exper. Med. **13:** 616, 1911.

[6] —: A study of tracings from the region near the apex of the heart. J. Exper. Med. **14:** 351, 1911.

[7] Wiggers, C. J.: Circulation in Health and Disease. Philadelphia, Lea and Febiger, 1923. P. 247.

[8] Dressler, W.: Die Brustwandpulsationen als symptome von Herz und Gefasskrankheiten. Wien, Verlag von Wilhelm Maudrich, 1933.

[9] Kountz, W. B., Gilson, A. S., and Smith, J. R.: The use of the cathode ray for recording heart sounds and vibration. I. Studies on the normal heart. Am. Heart J. **20:** 667, 1940.

[10] Smith, J. R., Gilson, A. S., and Kountz, W. B.: The use of the cathode ray for recording heart sounds and vibrations. II. Studies on the muscular element of the first heart sound. Am. Heart J. **21:** 17, 1941.

[11] Smith, J. R., Edwards, J. C., and Kountz, W. B.: The use of the cathode ray for recording heart sounds and vibrations. III. Total cardiac vibrations in one hundred normal subjects. Am. Heart J. **21:** 228, 1941.

[12] Kountz, W. B., and Wright, S. T.: Comparison of total vibrations obtained from a normal rapidly dying human heart with those obtained in chronic myocardial disease. Am. Heart J. **27:** 396, 1944.

[13] Rappaport, M. B., and Sprague, H. B.: The graphic registration of the normal heart sounds. Am. Heart J. **23:** 591, 1942.

[14] Miller, A., and White, P. D.: Crystal microphone for pulse wave recording. Am. Heart J. **21:** 504, 1941.

[15] Foulger, J. H., and Smith, P. E., Jr.: The differential heart sound meter. Indust. Med. **13:** 287, 1944.

[16] —, —, and Fleming, A. J.: Changes in cardiac vibrational intensity in response to physiologic stress. Am. Heart J. **34:** 507, 1947.

[17] —, —, and —: Cardiac vibrational intensity and cardiac output. Am. Heart J. **35:** 953, 1948.

[18] Mannheimer, E.: Calibrated phonocardiography. Am. Heart J. **21:** 151, 1941.

[19] Dunn, F. L., and Rahm, W. E., Jr: The visual study of heart vibrations and sounds as transmitted through the precordium. J. Insurance Med. **4:** (No. 3), 1949.

[20] Burger, H. C., and Koopman, L. J.: On the analysis and origin of heart sounds. Acta Cardiol. **4:** 131, 1949.

[21] McKusick, V. A.: Electrokymography in the diagnosis of chronic constrictive pericarditis. Paper presented at the annual Scientific Session of the American Heart Association, June 22, 1950.

Observations on the Electrocardiogram and Ventricular Gradient in Complete Left Bundle Branch Block

By J. F. PANTRIDGE, M.D.

Electrocardiograms from 109 patients with left bundle branch block were divided into four major groups depending on differences in standard and unipolar precordial leads. These records were then studied to find if one can draw any conclusions relative to ventricular hypertrophy or myocardial infarction in the presence of left branch block. In addition, the ventricular gradient was estimated in twenty-three instances and its value discussed.

WILSON and his associates[1, 2] have shown that in the absence of precordial leads it may be impossible to differentiate the various types of intraventricular block. Studies of bundle branch block in which the diagnosis is based on the standard limb leads alone are unsatisfactory since right- and left-sided defects in conduction cannot be separated with certainty.

The object of this study is to present the electrocardiographic and some of the clinical features of a series of cases in which from examination of the standard and six or more unipolar precordial leads, it was thought that left bundle branch block was present. It was considered worthwhile to ascertain the extent to which the presence of this conduction defect obscures electrocardiographic evidence of cardiac enlargement and of myocardial infarction.

The records of 160 patients were examined. Those in which the QRS interval of the standard limb leads was not definitely greater than .12 second and those in which leads from the right side of the precordium suggested the possibility of delay in activation of the right ventricle were discarded; 109 remained for detailed study. Each of these was placed in one of the following groups.

Group I—45 cases. These records were considered in every respect typical of left branch block. Lead I showed a monophasic positive QRS deflection, and unipolar leads from the left precordium showed a broad flat-topped or bifid R wave with peaks of approximately equal magnitude. The amplitude of these R waves was always considerably less than that of the S wave of the leads from the right precordium (fig. 1). The symbol N/2 indicates that tracings were taken with the electrocardiograph at one half the normal sensitivity.

Group II—6 cases. These differed from those in group I in that an S wave was present in lead I and in one or more leads from the left side of the precordium (fig. 2).

Group III—13 cases. These records showed Q waves in lead I, lead V_L or the leads from the left side of the precordium (fig. 3).

Group IV—11 cases. The complexes of the leads from the left precordium were not of the type usually obtained from points to the left of the transitional zone in left bundle branch block. Complexes of this usual type were found in 2 of these cases when additional leads were obtained from the left side of the thorax. In one case these complexes were obtained at the posterior axillary line, in the other at the angle of the left scapula. Two cases in this group showed S waves in lead I.

The transitional zone in the majority of the cases in this study lay between the points from which leads V_4 and V_5 were taken. The factors responsible for its displacement to the left in cases in this group are not clear. In some it may have been due to right ventricular enlargement. However, undoubted evidence of preponderant

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

Some of the observations reported in this article were made with the aid of a grant to Frank N. Wilson, M.D. from the S. S. Kresge Foundation.

enlargement of the right ventricle was obtained in only 2 of these 11 cases.

Group V—34 cases. One or more precordial leads taken from points to the left of the transitional zone showed atypical R waves. In the majority of cases in this group these atypical deflections were bifid but there was a gross inequality in the voltage of the two peaks (fig. 4; see V_5 and V_6). In a few, R showed more than one notch (fig. 5).

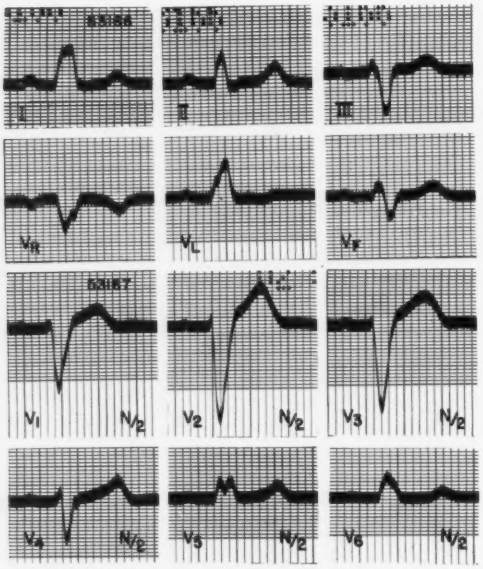


FIG. 1. An example of typical left bundle branch block (group I), heart in horizontal electrocardiographic position, in a 24 year old man without other evidence of heart disease. No digitalis. Precordial leads recorded at one-half the normal sensitivity (N/2).

CARDIAC ENLARGEMENT AND LEFT BUNDLE BRANCH BLOCK

The records of patients in groups I and II were studied with the object of ascertaining the relationship between the heart size and the magnitude of the deflections in the standard and precordial leads. The maximal deflections in leads I and III, the maximal depth of the S wave in leads from the right precordium, and the maximal height of the R wave in leads from the left precordium were measured, and the measurements were corrected for errors in standardization. The heart size was determined by radiologic examination which in the majority of instances included a 6 foot teleroentgenogram, an orthodiagram, and estimation of the cardiac area by the Hodges-Eyster method. Cardiac enlargement when present was classified as slight, moderate, or marked. The data

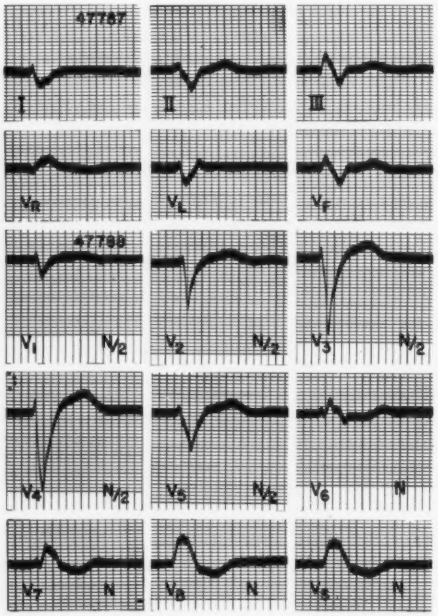


FIG. 2. Left bundle branch block with S waves present in lead I and in leads V_1 through V_5 (group II), heart in indeterminate electrocardiographic position. V_8 indicates a unipolar lead over the eighth dorsal spine; V_B a lead from the left interscapular region. Patient was a 72 year old white man with arteriosclerotic and hypertensive heart disease. Autopsy revealed insignificant changes in the coronary arteries, left ventricular hypertrophy and dilatation; microscopic examination showed hypertrophy of the cardiac fibers and marked patchy myofibrosis. Patient on digitalis.

obtained from this study are shown in table 1. It will be seen that if allowance is made for the higher incidence of cardiac failure in those with larger hearts and for the fact that radiologic examination gives but an approximate estimate of the true heart size, the magnitude of the deflections in the precordial leads gives a reasonably good indication of the presence and degree of cardiac enlargement. A comparison

of the records of hypertensive patients with those of patients without hypertension, shows that the average magnitude of the deflections in both the standard and precordial leads is considerably greater in the former (table 1, columns 6 and 7).

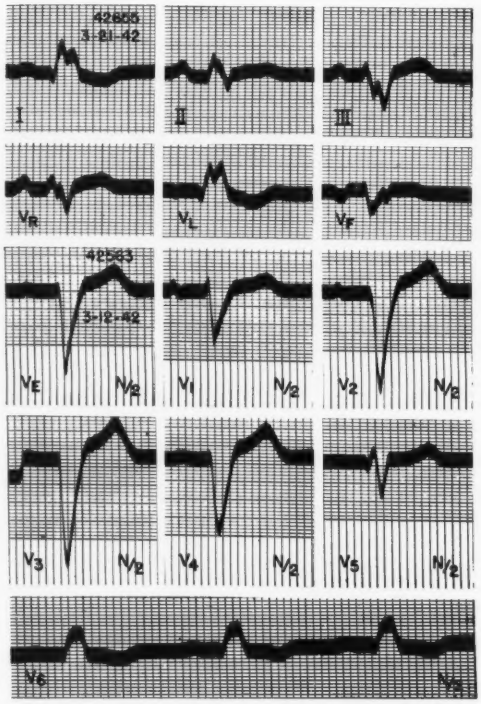


FIG. 3. Left bundle branch block with prominent Q waves in leads I, V_L, V_5 and V_6 (group III). Patient was a 66 year old Negro woman with arteriosclerotic and questionable syphilitic heart disease with far advanced heart failure and pericardial effusion. Patient had received digitalis.

MYOCARDIAL INFARCTION COMPLICATING LEFT BUNDLE BRANCH BLOCK

The difficulty of establishing the diagnosis of myocardial infarction in the presence of left bundle branch block is well known.[3, 5] It is due in large part to the fact that, with the exception of cases in which the interventricular septum is grossly involved, the potential of the cavity of the left ventricle is positive during the initial period of ventricular activation. Therefore Q waves associated with infarction and due to the transmission of the initial negative potential of

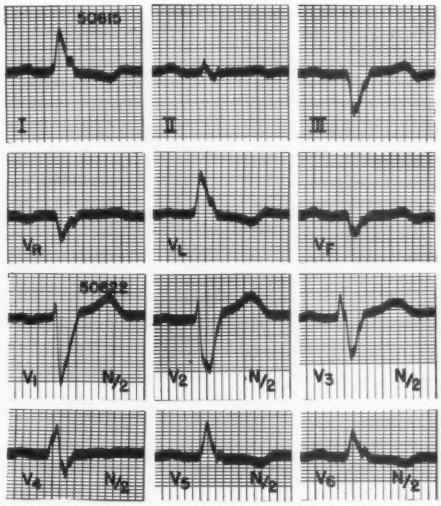


FIG. 4. Left bundle branch block with atypical R waves in the leads from the left precordium (group V). Heart in horizontal electrocardiographic position. Patient was a 79 year old white man with arteriosclerotic heart disease. No digitalis.

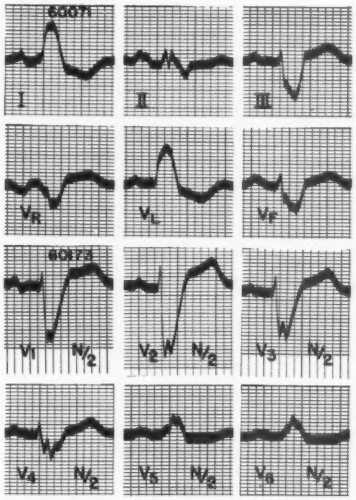


FIG. 5. Left bundle branch block with atypical R waves from the left precordium (group V). Heart in horizontal electrocardiographic position. A 71 year old white man with arteriosclerotic heart disease. On digitalis.

the left ventricular cavity through the infarcted area do not occur. However, when the septum is grossly involved, the potential of the cavity of the right ventricle which is initially

negative in left bundle branch is transmitted to the cavity of the left ventricle. Left bundle branch block complicated by an infarct involving both the free wall of the left ventricle and the interventricular septum and extending through the greater part of the thickness of a portion of the latter, would therefore be expected to show Q waves in those leads which reflected the potential of the epicardial surface of the infarcted wall of the left ventricle. The records of cases in group III, those showing Q waves in leads I, V_L or in leads from the left precordium, were for this reason subjected to critical study. A QS deflection in lead III has been omitted from the discussion since it has been seen in cases where the possibility of infarction could be excluded.

The presence of Q waves in leads I and V_L does not necessarily indicate infarction with septal involvement since these deflections might be expected if the heart were so placed that the initial negative potential of the cavity of the right ventricle was transmitted to the left arm. In this connection it may be noted that the incidence of a Q wave in lead I is much higher in experimental left bundle branch block in the dog than in clinical left bundle branch block.[4] This is undoubtedly due to the more vertical position of the dog's heart.

In left bundle branch block there are often no R waves in the leads from the right side of the precordium. When these deflections are absent and the transitional zone is displaced to the left, Q waves found in leads V_5 and V_6 may represent the transmission to the left side of the precordium of the potential variations responsible for the QS deflections of the leads from the right side; that is to say, the complexes of leads V_5 and V_6 in such cases are transitional in type and represent a mixture of potential variations of the kind that occur at points farther to the left and potential variations that occur at points farther to the right. The presence of an R wave in lead V_1 and its diminution or disappearance in leads V_2,V_3, and V_4 in association with Q waves in leads from the left precordium is, however, suggestive of anteroseptal infarction (table 2, cases 51, 64, 90, and fig. 3). The relations between the presence of Q waves in the leads considered, the absence of R waves in leads from the right precordium and the clinical impression of the probability or possibility of myocardial infarction in the cases placed in group III are shown

TABLE 1. *Relationship between Heart Size and Magnitude of Deflections in Standard and Precordial Leads.*

Heart Size		Normal	Slightly Enlarged	Moderately Enlarged	Markedly Enlarged	Patients with Hypertension	Patients without Hypertension
I +III	Max.	21.5	33	22.5	34	38.5	21.5
	Av.	−12.4	17.5	11.4	14.7	18.8	12.5
	Min.	6.5	5	6.5	7	7.0	5.0
S	Max.	46	68	76	80	80.0	64
	Av.	33.3	43.5	42.5	47.5	53.2	35.8
	Min.	18	22	15	25	29.0	15
R + S	Max.	60	82	90	117	117.0	83
	Av.	44.5	57	57.1	62	69.3	46.6
	Min.	33	34	18	28.5	39.0	18
QRS	Max.	0.16	0.18	0.16	0.16	0.18	0.16
	Av.	0.144	0.152	0.146	0.143	0.150	0.143
	Min.	0.12+	0.12+	0.12+	0.12+	0.12+	0.12+

I + III = The sum of the maximal deflection in lead I and the maximal deflection in lead III.
S = The maximal depth of the S wave in the leads from the right side of the precordium.
R + S = The sum of the maximal R wave from the left precordium and the maximal S wave from the right precordium. The measurements are expressed in millimeters at normal standardization.
QRS = The duration of the QRS interval in seconds.

in table 2. It will be seen that in only 4 cases (51, 64, 90, 105) did the electrocardiographic findings indicate the probability of myocardial infarction with septal involvement and that in only 2 did the clinical history support the impression obtained from the electrocardiogram.

The order of excitation of the ventricles in left bundle branch block is such that the initial peak of the usual bifid R wave in leads from the left side of the transitional zone may be expected to represent the arrival of the excitation wave at the left side of the septum. The final peak of the R wave in these leads represents in all probability the arrival of the excitation wave at the epicardial surface of the left ventricle immediately beneath the exploring electrode. Atypical complexes in leads from the left side of the transitional zone might therefore be associated with infarction of the septum or free wall of the left ventricle. Those in which the magnitude of the second peak is much smaller than that of the initial peak may result from damage of that part of the free wall of the left ventricle which lies immediately beneath the exploring electrode. Septal damage of insufficient extent to produce Q waves in the left precordial leads might cause a diminution in the magnitude of the primary peak of the R wave in these leads. For these reasons the incidence of infarction in cases of left branch block with typical complexes in the left precordial leads (groups I and II) was compared with its incidence in cases in which these complexes were atypical (group V). This comparison is largely on the basis of clinical data. However, it will be seen from table 3 that the difference in the incidence of infarction in the two groups is probably significant.

TABLE 2. *Probable Incidence of Myocardial Infarction (Based on Clinical Impressions) Related to Occurrence of Q Waves and Absence of R Waves in Certain Leads*

Case No.	Position of Q Wave			Leads with R waves Absent	Clinical Impression Relating to Infarction
	Left Precordium	V_L	Lead I		
10	—	+	+	—	—
29	—	*	+	—	—
45	—	+	+	—	—
51	V_5 and V_6	+	+	V_2, V_3, V_4 (R present in V_1).	—
53	—	+	+	—	—
60	—	+	−	—	—
61	—	+	+	V_1, V_2, V_3	Possible
64	V_5 and V_6	*	+	V_4 (R present in V_1, V_2, V_3).	Typical History
80	—	+	+	V_1	—
90	V_5 and V_6	*	+	V_4 (Present V_1. Diminishing through V_2 and V_3)	—
92	—	*	+	V_1, V_2, V_3, V_4	Probable
102	—	+	+	—	—
105	V_5	+	+	—	Probable

* V_L not recorded.

TABLE 3.—*Probable Incidence of Myocardial Infarction Related to the Existence of Typical or Atypical QRS Complexes in Precordial Leads Taken to the Left of the Transitional Zone.*

Groups	No. of Cases	Evidences of			Total
		Infarction	Probable Infarction	Possible Infarction	
I and III	51	3	2	5	10
V	32	7	4	5	16

This view would be supported if additional leads from the left side of the precordium were obtained from patients in whom the usual precordial leads yielded complexes typical of left bundle branch block. A few of these patients might be expected to have infarction of the free wall of the left ventricle in regions not explored by the usual precordial leads. If, then, atypical complexes in which the second peak of the bifid R wave was much smaller than the

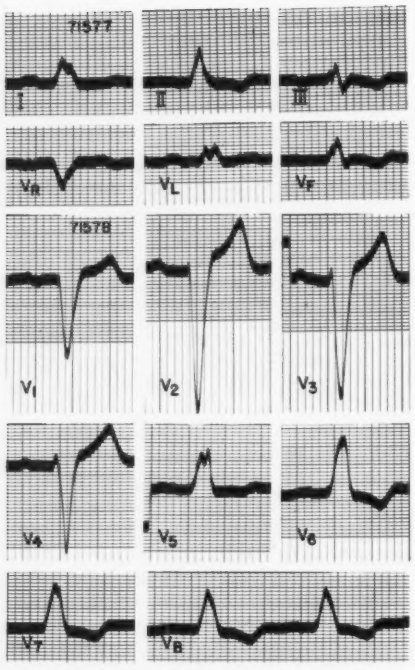


FIG. 6. Left bundle branch block (group I). Heart in intermediate electrocardiographic position. A 59 year old white woman with diabetes mellitus and arteriosclerotic heart disease.

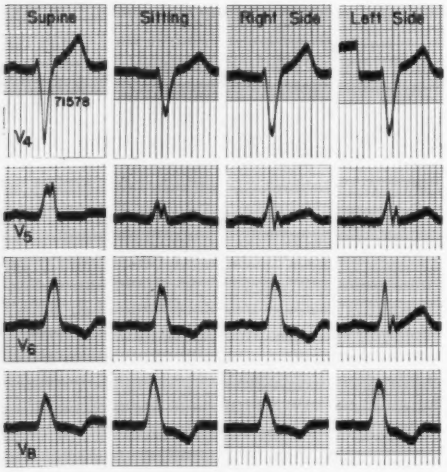


FIG. 7. Leads V_4, V_5, V_6 and V_8 of same patient as figure 6 recorded with patient in various positions as indicated. See text.

primary peak were obtained on further exploration of the left precordium, this would suggest that the exploring electrode had been placed over the infarcted area.

Information of the type under consideration was obtained during a study of the effect of position of the heart on the precordial electrocardiogram in left bundle branch block. It was noted that in some patients the character of the complexes obtained in leads from the left side of the transitional zone was not affected by alteration of the position of the patient while the precordial leads were recorded, and that in others typical complexes in these leads were converted to those of an atypical form.

Figure 6 shows the limb and precordial leads in a case with typical left bundle branch block recorded with the patient in the usual recumbent position. Figure 7 shows the marked alteration that occurred in the secondary R waves in the leads V_5 and V_6 when these leads were recorded with the patient in different positions. Leads V_4, V_5, V_6, and V_8 were recorded in the supine, in the sitting, in the right lateral, and in the left lateral positions. The secondary R waves in leads V_5 in the sitting, right and left lateral positions and those of lead V_6 in the left lateral position, occur as a notch at the base of the descending limb of the primary R wave. These secondary R waves closely resemble those of leads V_5 and V_6 in figure 4.

It has been suggested that records of the type in which the initial R in lead I and in the leads from the left precordium is peaked and shows a broad notch on its descending limb represent focal left-sided block of major degree. Since, however, waves of this type may be found on additional exploration of the left precordium in patients with typical left bundle branch block, it is possible that in some cases they indicate damage of the free wall of the left ventricle.

THE VENTRICULAR GRADIENT IN COMPLETE LEFT BUNDLE BRANCH BLOCK

It has been shown that the order of activation of the ventricular myocardium is not likely to affect either the magnitude or the direction of the vector which represents the lack of uniformity in the duration of its excited state.[6–8] Accurate determination of this vector might therefore be expected to yield some elec-

trocardiographic information which is obscured by the presence of left bundle branch block.

This vector, the ventricular gradient, was determined in 23 cases in this series. An attempt was first made to estimate from clinical examination the extent of the myocardial damage in the cases selected. In a few the results of postmortem examination were available. On the basis of this estimation of the degree of myocardial damage the cases were divided into the following four groups: (a) Minimal myocardial disease. (b) Slight or moderate myocardial disease. (c) Grave myocardial disease without clinical or pathologic evidence of infarction. (d) Probable or proved myocardial infarction. With the exception of 3 cases in which electronic integrated electrocardiographic records were available, the following method was used in this study. A ventricular complex was selected from each standard lead at a portion of the tracing where the base line shift was minimal. Particular care was taken to ensure that the complexes selected were those recorded at approximately the same phase of respiration. Each complex was then enlarged six to eight times by means of a photographic enlarger. The recorded areas of the QRS and T components of each complex are each an average of three planimeter readings. The algebraic sum of the areas of QRS and T in each lead gave the magnitude of the QRS-T or ventricular gradient, G, in that lead. The sum of the readings in leads I and III seldom exactly equalled that in lead II. These readings were adjusted to their most probable values by adding to lead II and subtracting from leads I and III the quantity X, which is defined as the algebraic sum of leads I and III less lead II.[10] The adjusted readings were used when calculating the mean electrical axis and the manifest area of QRS, T, and G. It was then possible to estimate roughly the error in the calculated magnitude and direction of these vectors in terms of the magnitude of X.[10] When M represents the magnitude of the vector in millivolt seconds, $\frac{+X}{50\ M}$ (degrees) is approximately twice the probable error in the calculated direction of the vector and $\frac{+X}{M}$ per cent is roughly twice the probable error in its magnitude provided the measurement errors are random. The term "probable error" is used in its customary statistical sense. The actual error will exceed twice the probable error in approximately 20 per cent of the calculations. The more important clinical features, the mean electrical axis and the manifest area of the QRS, T, and G of the selected patients are shown in table 4. The range of error, defined as twice the probable error in these determinations, and the ratio between the manifest areas of G and QRS are also shown.

It will be seen that in some cases the range of error is considerable. In case 13 the range of error in the direction of the gradient is 20 degrees. Five cases, in which the range of error in the determination of the gradient was greater than this, were excluded from this study. Since measurement of the area beneath the ventricular deflections by a planimeter is the most accurate visual method of determining the ventricular gradient, it is apparent that the error in determining this vector by the more rapid visual methods may be gross.

Vectors representing the position of the mean electrical axis and the manifest area of G and QRS have been plotted in figure 8.

In cases 1–3 (fig. 8*A*), which are considered examples of minimal myocardial disease, G is in magnitude and direction within the limits at present regarded as normal.[12–14]

In 2 out of 5 cases regarded as examples of slight or moderate myocardial disease, G is grossly abnormal (cases 4–9, fig. 8*B*). In case 8, it is abnormal, because of its direction (−62.5°) and in case 9, because of the magnitude of the angle between G and QRS (92.5°). The magnitude and the G:QRS ratio in the latter case are also markedly reduced. This may, however, be due to digitalis.

Each of the 5 cases with clinical or pathologic evidence of grave myocardial disease show an abnormal ventricular gradient (fig. 8*C*). In case 11, G is grossly abnormal in direction (−60°). The remaining cases in this group show an abnormally small G and G:QRS ratio. These patients may have received digitalis.

In all 4 cases with probable myocardial infarction, G is markedly abnormal (fig. 8*D*). In

TABLE 4. *Summary of Clinical Information from 18 Selected Patients Where the Ventricular Gradient Was Measured.*

No.	Age	Diagnosis	BP	Heart Size	Evidence of Failure	History of Infarction	Digitalis	Heart Rate		α	M	E_{ai}	EM%	M-QRST/QRS
1	24	Functional systolic murmur	114/68	Normal	—	—	−	76	QRS	−10	69	3	5	
									T	75	42	5	10	1.2
									QRST	19	84	5	9	
2	56	Cholecystitis. No apparent cardiac abnormality.	—	Normal	—	—	−	97	QRS	−9	69	6	11	0.8
									T	122	36	11	23	
									QRST	21	53	15	29	
3	35	Thyrotoxicosis	132/78	Normal	—	—	−	65	QRS	38	37	2	4	
									T	20	28	11	22	0.6
									QRST	31	64	6	12	
4	72	Myxedema	120/80	Normal	—	—	−	68	QRS	−14	108	1	1	
									T	146	36	9	18	1.7
									QRST	4	75	4	7	
5	37	Essential hypertension Cholecystitis	154/102	? slight enlargement	—	—	+	88	QRS	2	71	5	9	
									T	−176	32	4	8	0.58
									QRST	0	41	5	10	
6	39	Rheumatic heart disease. Mitral stenosis	120/90	? slight enlargment	—	—	+	75	QRS	6	89	1	2	
									T	−159	45	5	10	0.53
									QRST	−8	47	4	8	
7	71	Arteriosclerotic heart disease. Hypertension. Death from bronchopneumonia. P. M. heart weight 400 Gm. No evidence of infarction.	105/100	Slight enlargement	—	—	+	78	QRS	22	36	11	19	
									T	99	20	30	60	1.2
									QRST	47	45	12	24	
8	49	Chronic Nephritis	232/126	Moderate enlargement	—	—	+	73	QRS	−62	181	4	8	
									T	123	101	1	2	0.45
									QRST	−69	81	7	14	
9	82	Carcinoma of bladder, postoperative death. P.M. patchy myocardial fibrosis	128/69	Moderate enlargement, 486 Gm.	—	—	+	79	QRS	−55	61	1	1	
									T	111	72	1	1	0.19
									QRST	37	11	4	10	
10	74	Arteriosclerotic heart disease	118/50	Moderate enlargement	Moderate congestive, failure	—	+	107	QRS	22	33	6	12	
									T	−151	21	15	30	0.36
									QRST	10	12	4	8	
11	72	Arteriosclerotic heart disease	140/90	Moderate enlargement	Mild congestive failure	—		65	QRS	−65	220	2	4	
									T	112	153	3	6	0.30
									QRST	−60	67	1	1	

12	60	Arteriosclerotic heart disease. Angina pectoris. P.M. gross myocardial scarring	200/100	Moderate enlargement, 480 Gm.	—	—	+	54	QRS T QRST	−76 80 −26	41 33 17	1 3 5	1 5 9	0.42
13	74	Arteriosclerotic heart disease	130/75	Normal	—	P.M. Gross fibrosis left ventricle. Coronary vessels patent	+	77	QRS T QRST	29 −154 39	35 23 12	4 17 20	8 34 40	0.35
14	57	Rheumatic heart disease. Hypertension. Pulmonary tuberculosis.	170/90	Moderate enlargement	Moderate congestive failure	Suggestive	+	70	QRS T QRST	42 −136 –	57 57 —	1 4 —	1 8 —	0.03
15	65	Arteriosclerotic heart disease	122/86	Slight enlargement	Moderate congestive failure	Highly suggestive history	+	72	QRS T QRST	−62 109 −24	87 75 16	1 1 10	2 2 20	0.19
16	59	Arteriosclerotic heart disease	126/90	Marked enlargement, 750 Gm.	Gross congestive failure	P.M. Old infarction involving the apex with mural thrombosis	+	102	QRS T QRST	−64 123 −81	68 47 21	4 1 12	8 1 23	0.31
17	53	Arteriosclerotic heart disease	140/103	Marked cardiac enlargement	Mild congestive failure	Two typical clinical attacks	−	100	QRS T QRST	−36 138 7	36 33 4	3 11 13	6 21 25	0.13
18	49	Essential hypertension	226/122	Slight enlargement	—	Two fairly typical attacks	−	94	QRS T QRST	−52 115 −45	103 38 67	9 2 14	18 4 28	0.65

α = The angle in the triaxial reference system
M = The magnitude in millivolt seconds (4mv. = 1 unit)
Eα = The range of error in estimating the angle (twice the probable error)
EM% = Range of error in estimating the magnitude

$$\text{M QRST/QRS} = \frac{\text{magnitude QRST}}{\text{magnitude QRS}}$$

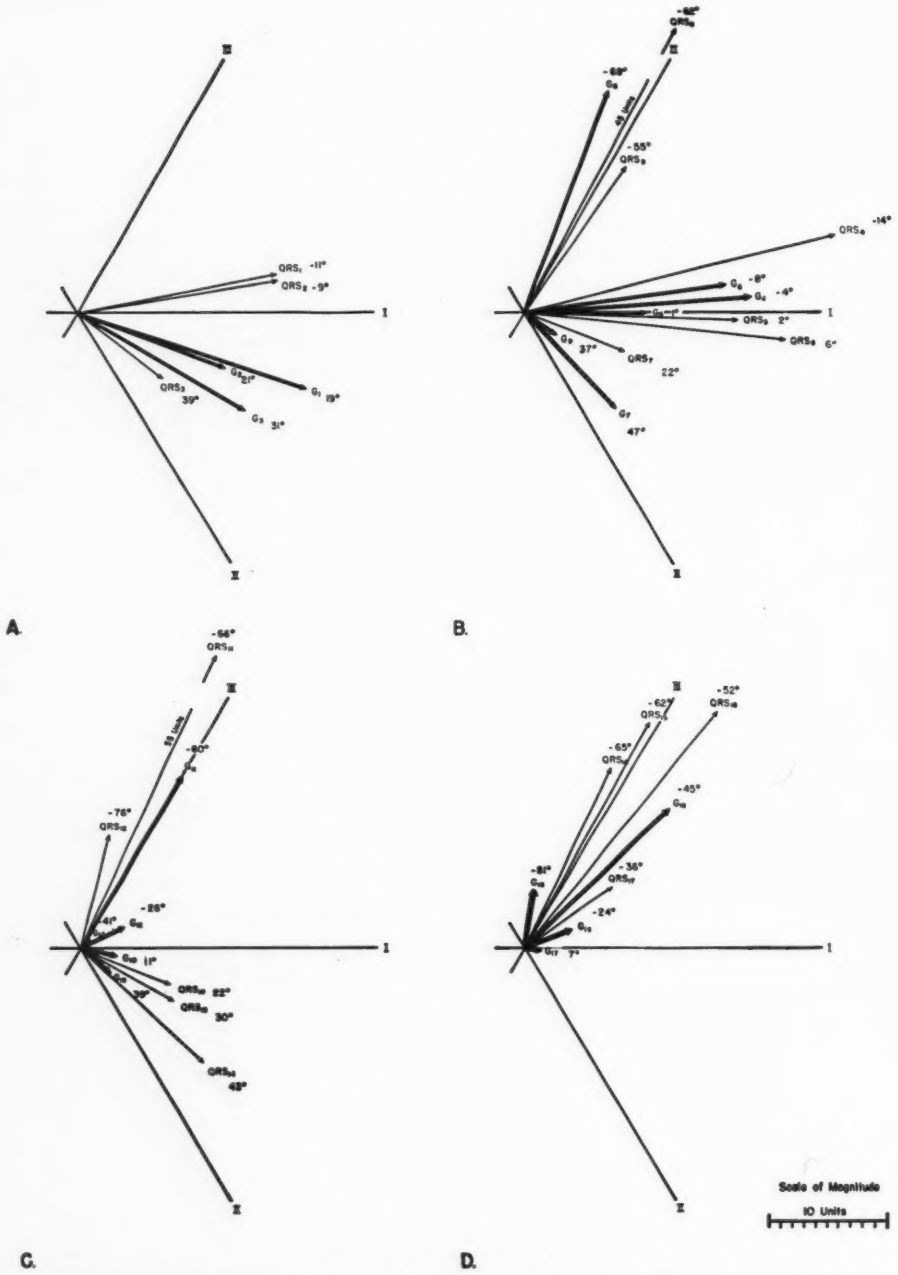


FIG. 8. Diagram of the QRS and G vectors of cases with (*A*) minimal (*B*) slight or moderate, and (*C*) grave myocardial disease, and (*D*) cases with probable myocardial infarction.

cases 16 and 18 it is abnormal in direction (−81° and −45°) and in cases 15 and 17 it is markedly reduced in magnitude and the G:QRS ratio is small. Digitalis can be excluded as the

cause of the reduction of the magnitude of G and G:QRS ratio in case 17.

Summary

A study of the electrocardiogram in cases of complete left bundle branch block shows that the presence of this conduction defect does not obscure the evidence of left ventricular enlargement in the precordial electrocardiogram.

The usual electrocardiographic evidence of myocardial infarction is with few exceptions completely obscured by left bundle branch block. Variations in the form of the QRS complex in leads from the left side of the transitional zone in left bundle branch block are described. The significance of these variations in relation to the diagnosis of myocardial infarction is discussed.

The ventricular gradient has been determined in 18 cases of complete left bundle branch block. The results support the belief based on theoretic and experimental evidence that changes in the magnitude and direction of this vector will reveal electrocardiographic information usually obscured by this conduction defect. Despite the use of greatly enlarged records and an accurate planimeter the sum of the areas in leads I and III did not always closely approximate that of lead II. This implies large uncertainties (probable errors) in the calculated magnitude and direction of the ventricular gradient and indicates the difficulty in determining these quantities precisely.

Acknowledgments

The author wishes to express his appreciation to Dr. Frank N. Wilson for his help in the preparation of this paper and also to Dr. Franklin D. Johnston, Dr. J. Marion Bryant, and Mr. Richard McFee.

REFERENCES

[1] Wilson, F. N., McLeod, A. G., and Barker, P. S.: Order of ventricular excitation in human bundle branch block. Am. Heart J. **7:** 305, 1932.

[2] —: Concerning the form of the QRS deflections of the electrocardiogram in bundle branch block. J. Mt. Sinai Hosp. **8:** 1100, 1942.

[3] —, Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menzes de Oliveira, R., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[4] —: Unpublished observations.

[5] Rosenbaum, F. F., Erlanger, H., Cotrim, N., Johnston, F. D., and Wilson, F. N.: The effects of anterior infarction complicated by bundle branch block upon the form of the QRS complex of the canine electrocardiogram. Am. Heart J. **27:** 783, 1944.

[6] Segers, M.: The different types of intraventricular block. Am. Heart J. **37:** 92, 1949.

[7] Wilson, F. N., and Herrman, G. R.: An experimental study of incomplete bundle branch block, and of the refractory period of the heart of the dog. Heart **8:** 229, 1921.

[8] —, and Finch, R.: The effect of drinking iced water upon the form of the T deflection of the electrocardiogram. Heart **10:** 275, 1923.

[9] —, McLeod, A. G., Barker, P. S., and Johnston, F. D.: Determination and significance of the areas of the ventricular deflections of the electrocardiogram. Am. Heart J. **10:** 46, 1934.

[10] McFee, R.: Comparison of heart vectors calculated with different systems of leads. Circulation **2:** 128, 1950.

[11] Ashman, R., Byer, E., and Bayley, R. H.: The normal human ventricular gradient. I. Factors which affect its direction and its relation to the mean QRS axis. With appendix on notation. Am. Heart J. **25:** 16, 1943.

[12] —, and —: The normal human ventricular gradient. II. Factors which affect its manifest area and its relationship to the manifest area of the QRS complex. Am. Heart J. **25:** 36, 1943.

[13] —, Gardberg, M., and Byer, E.: The normal human ventricular gradient. III. The relation between anatomic and electrical axis. Am. Heart J. **26:** 473, 1943.

[14] —: The normal human ventricular gradient. IV. The relationship between the magnitudes, A_{QRS} and G, and deviations of the RS-T segments. Am. Heart J. **26:** 495, 1943.

The Spatial Vectorcardiogram in Right Bundle Branch Block

By J. A. Abildskov, M.D., C. E. Jackson, M.D., G. E. Burch, M.D., and J. A. Cronvich, M.S.

The spatial vectorcardiograms of 24 subjects with electrocardiographic evidence of right bundle branch block are described. Correlation of the vectorcardiographic patterns observed, with clinical and roentgenologic data, suggests that the recognition of ventricular hypertrophy in the presence of such a conduction defect may be improved by this method of study.

ALTHOUGH characteristic electrocardiographic features identify most cases of right bundle branch block, evidence of associated myocardial lesions may be masked by the prolonged QRS complex and resultant secondary T-wave changes. Infarction can usually be recognized by changes in the initial portion of the QRS complex, which is not significantly altered by this conduction defect, but other myocardial abnormalities result in changes in later portions of the QRS, the S-T segment and the T wave, all of which are grossly affected by right bundle branch block. In our experience, electrocardiographic evidence of ventricular hypertrophy is often lacking even when clinical and roentgenologic examinations indicate its presence.

The present study of right bundle branch block was designed to investigate the possibility that three-dimensional vectorcardiography might provide information concerning the state of the myocardium which is not apparent from the electrocardiogram as currently used.

Materials and Methods

Twenty-four subjects whose electrocardiograms fulfilled the conventional criteria for diagnosis of right bundle branch block were selected for study. The pertinent clinical data are summarized in table 1. The electrocardiograms of all subjects showed a QRS duration of 0.12 second or more in the standard leads, all but three showed broad S waves in lead I, and all had large bifid or slurred R waves in leads from the right side of the precordium. Subjects whose electrocardiograms were in any way atypical of right bundle branch block were not included in this report.

Eighteen subjects had roentgenologic evidence of left ventricular hypertrophy. Of these, 10 had diastolic hypertension, 1 had syphilitic aortic insufficiency, 1 had cardiac disease of unknown etiology and the remaining 6 were considered to have arteriosclerotic heart disease. Subjects 9, 16, 17 and 18 (fig. 1) had electrocardiographic evidence of anterior myocardial infarction. Subject 13 died following prostatectomy and postmortem examination of the heart revealed moderate left ventricular hypertrophy. The heart weighed 450 Gm., and the left and right ventricular walls measured 20 mm. and 6 mm., respectively. Three subjects, 2 with cor pulmonale and 1 with an interatrial septal defect, had right ventricular enlargment and little or no enlargement of the left ventricle. Three subjects had no clinical or roentgenographic evidence of cardiac enlargement. One had arteriosclerotic heart disease, and in the other 2, right bundle branch block was the only evidence of cardiac disease.

Projections of the spatial vectorcardiograms on frontal, sagittal, right, left and superior planes of the equilateral tetrahedral reference system were photographed from cathode ray oscilloscopes. The oscilloscopic trace was interrupted at approximately 1/600 second intervals to indicate time. Simultaneously recorded frontal and sagittal projections were utilized to construct wire models representing the spatial vectorcardiograms. Accuracy of the models was checked against the projections recorded from right, left and superior planes of the tetrahedron. Details of the methods employed appear in previous publications from this laboratory.[1, 2] A few of the subjects were also studied by a recently described method of recording stereoscopic views of the spatial vectorcardiogram directly from two cathode ray oscilloscopes.[3]

Recent electrocardiograms, including standard

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans, and the Department of Medicine, Tulane University School of Medicine and School of Electrical Engineering, Tulane University, New Orleans, La.

Aided by grants from the Life Insurance Medical Research Fund, a War Department Grant No. W-49-007-MD-389, the Mrs. E. J. Caire Fund for Research in Heart Disease, and a Public Health Service grant.

leads and precordial leads V_1 to V_6, were obtained in all instances, and unipolar leads from the limbs and back were available in most cases.

The form, direction of inscription and direction of axis of the QRS sÊ-loops have been studied. The term, axis of the loop, is used to indicate a line drawn from its origin to its most distant point and bears no constant relation to the electrical axis in the electrocardiogram. Angles were measured on the triaxial reference system in the frontal plane and in a similar manner in the sagittal plane with the ±180 degree axis located anteriorly.[1, 2]

TABLE 1.—*Clinical Data*

Subject No.	Age	Sex	Cardiac Enlargement*	B.P.	Myocardial Infarction	Cardiac Diagnosis†
			A. *Adult Subjects with Left Ventricular Enlargement*			
1	58	M	+	180/120	−	H.C.V.D.
2	76	M	++	180/120	−	A.S.H.D. and H.C.V.D.
3	69	F	++	110/70	−	A.S.H.D.
4	55	F	++	160/90	−	H.C.V.D.
5	48	M	+++	160/90	−	A.S.H.D.
6	61	M	+++	180/90	−	A.S.H.D.
7	52	M	+	140/86	−	A.S.H.D.
8	50	F	+++	170/100	−	Syphilitic Heart Disease
9	60	M	+++	136/80	+	A.S.H.D.
10	50	M	+	130/75	−	Heart Disease of Unknown Etiology
11	59	M	+	162/102	−	H.C.V.D.
12	61	M	++	220/120	−	H.C.V.D.
13	73	M	++	210/110	−	A.S.H.D. and H.C.V.D.
14	59	M	++	240/120	−	A.S.H.D. and H.C.V.D.
15	66	M	++	160/100		H.C.V.D. and A.S.H.D.
16	61	M	++	112/70	+	A.S.H.D.
17	67	M	++	180/85	+	A.S.H.D.
18	71	M	++	180/110	+	H.C.V.D. and A.S.H.D.
			B. *Adult Subjects with Right Ventricular Enlargement*			
19	45	M	+	142/86	−	Cor pulmonale
20	31	F	+++	90/60	−	Lutembacher's Syndrome
21	68	M	+++	120/60	−	Cor pulmonale
			C. *Adult Subjects with No Enlargement*			
22	54	M	−	100/60	−	Normal
23	62	M	−	116/90	−	Carcinoma of stomach
24	78	M	−	170/90	−	A.S.H.D.

* Cardiac Enlargement: + = moderate, ++ = moderately severe, +++ = severe.
† H.C.V.D. = Hypertensive cardiovascular disease.
A.S.H.D. = Arteriosclerotic heart disease.

RESULTS

Subjects with Left Ventricular Hypertrophy. Drawings made from the simultaneously recorded frontal and sagittal projections of the QRS sÊ-loops of the 18 subjects with left ventricular hypertrophy are shown in figure 1. Most of these records show considerable similarity. In the frontal plane all were inscribed in a counterclockwise direction and in most instances they enclosed wide areas. In the sagittal plane 11 were inscribed clockwise and 7 counterclockwise. The areas enclosed by the sagittal plane projections were relatively narrow. The axes of these loops, with the exception of that of subject 1, lay between −5 and −90 degrees in the frontal plane and between −20 and −175 degrees in the sagittal plane. The exception noted had a frontal plane axis of +50 degrees and an axis in the sagittal

plane of +120 degrees. As can be noted in figure 1, all records in this group had fairly smooth, rounded contours of that portion of the QRS sÊ-loop situated to the left of the isoelectric point in the frontal plane.* That part of the record lying to the right of the isoelectric point was variable as to area, but in all cases the trace moved relatively slowly while this section was being inscribed. The contour of this portion of the records was also variable and in three instances, subjects 7, 9 and 13 (fig. 1), there were striking irregularities.

The axes were positive in the frontal and sagittal planes, varying between +50 and +100 degrees. The records of the subjects in this group were irregular in contour and that of subject 21 had extensive indentations of the terminal portions of the QRS sÊ-loop. The largest area enclosed by the frontal plane QRS sÊ-loop was located to the right of the isoelectric point in each case.

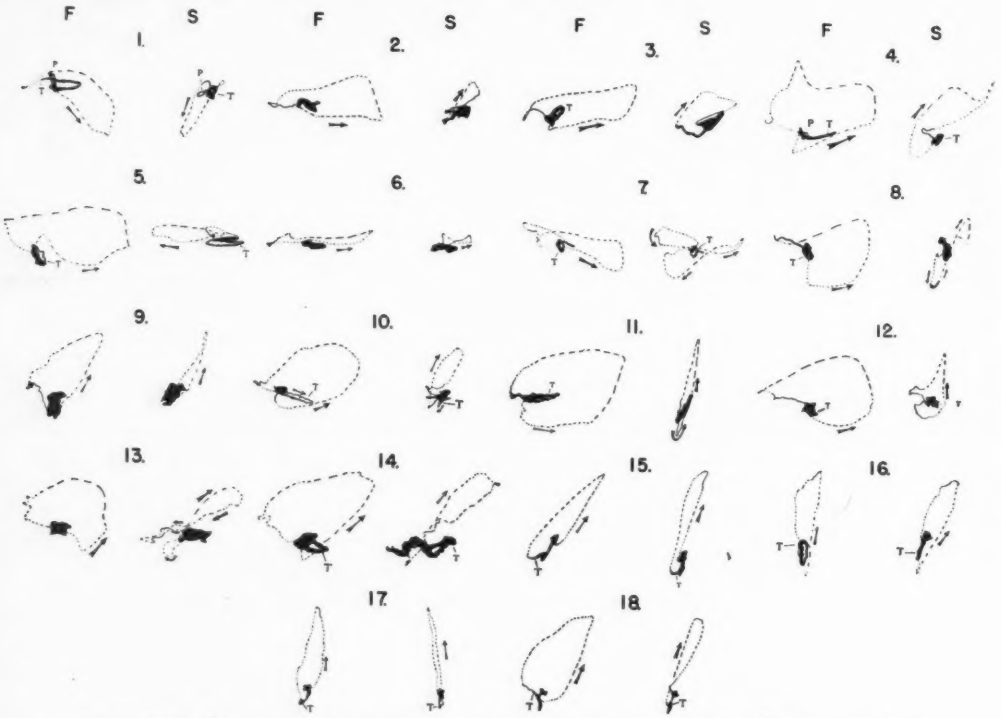


FIG. 1. QRS sÊ-loops of subjects with left ventricular enlargement. P and T sÊ-loops may be identified in several of the records.

Subjects with Right Ventricular Hypertrophy. Frontal and sagittal projections of the spatial vectorcardiograms of the 3 subjects with right ventricular hypertrophy are shown in figure 2. Two of these were inscribed in a clockwise and one in a counterclockwise direction in the frontal plane. In the sagittal plane one was inscribed counterclockwise and two clockwise.

The records shown in figure 3 were obtained from 3 subjects; 2 had no evidence of cardiac disease other than right bundle branch block and the other (subject 24) was a subject with coronary arteriosclerosis without cardiac enlargement. Subject 22 had intermittent right bundle branch block. In figure 3, *A* and *B* represent, respectively, normal conduction and conduction with the right bundle branch blocked in this subject. It will be noted that except for the terminal portion, which undoubtedly represents activation of the right ventricle in the case of *B*, the contour of these

* All directions are given in the conventional manner, in terms of the subject.

QRS sÊ-loops is similar. The frontal plane projection of each of the QRS sÊ-loops in this group was inscribed in a counterclockwise direction. Two were inscribed counterclockwise and 1 clockwise in the sagittal plane. The axes of the loops of subjects 22 and 23 were +60 degrees in the frontal plane and between +110 and +120 in the sagittal plane. The QRS sÊ-loop of the other subject of this group had a long limb extending to the right of the isoelectric point, with an axis, as defined, of −120 degrees in the frontal and −65 degrees in the sagittal plane. The axis of the initial portion, however, was +60 degrees in the frontal and +120 degrees in the sagittal plane.

The electrocardiograms of 1 subject from each group are shown in figure 4, and stereoscopic photographs of wire models representing the QRS sÊ-loops of the same subjects are shown in figure 5.

Discussion

Since the number of records studied is small and because pathologic examination has been obtained in only 1 of the subjects of this study, no more than tentative conclusions can be drawn.

With one exception (subject 1), the records obtained from subjects with left ventricular hypertrophy, as determined by clinical and

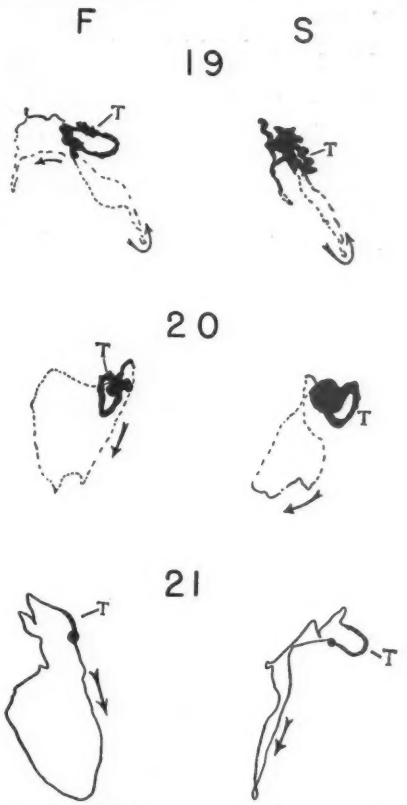


FIG. 2. QRS sÊ-loops and T sÊ-loops of subjects with right ventricular enlargement.

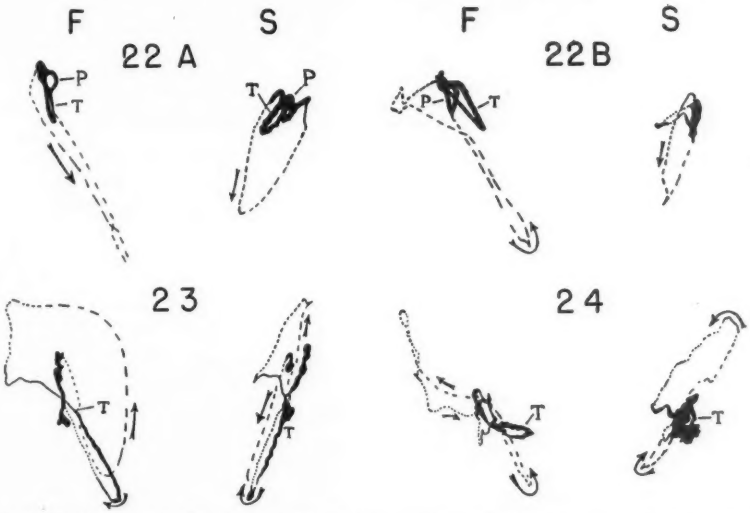


FIG. 3. QRS sÊ-loops and T sÊ-loops of subjects with no cardiac enlargement. Records 22*A* and 22*B* are from a subject with intermittent right bundle branch block; *A* showing normal conduction and *B* right bundle branch block.

radiologic means, were strikingly similar to each other, and, in their initial portions, to records obtained from subjects with left ventricular hypertrophy without bundle branch block. The electrocardiograms of only 5 of these subjects had been previously interpreted as suggestive of left ventricular hypertrophy, although most indicated myocardial abnormalities. Theoretically, the ventricular gradient would be useful in evaluating the state of the myocardium when this conduction disturbance is present. In practice, however, the vector of the net area of the QRS in many of these records is small and with available methods of estimating the gradient the error may be significant under these circumstances.[4] The similarity in form of 17 of the 18 records obtained from patients with left ventricular hypertrophy associated with right bundle branch block offers encouragement that vectorcardiographic methods may be useful in distinguishing this combination of lesions.

Records obtained from 3 subjects with isolated right ventricular hypertrophy and right bundle branch block were characterized by having the greater portion of the area enclosed by the QRS sÊ-loop to the right of the isoelectric point. The direction and contour of the initial portion of the QRS sÊ-loops in this group were similar to the records obtained from normal subjects. All of these subjects showed evidence of congestive failure. Subject 21, a 68 year old Negro man with cor pulmonale, had especially severe failure which had been present for over six years. The vectorcardiogram of this subject was distinguished by extreme irregularities of the terminal portion of the QRS sÊ-loop, which may, under these circum-

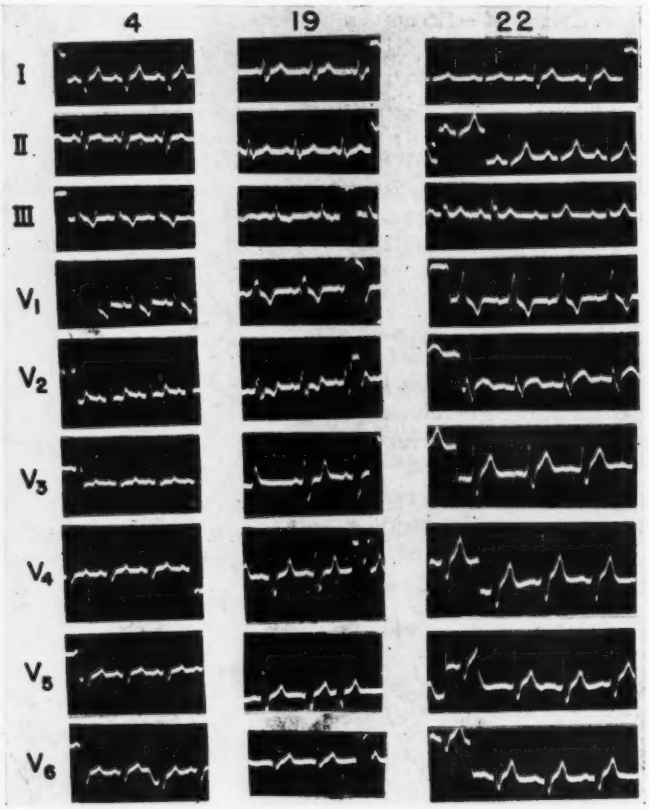


FIG. 4. Electrocardiograms of representative subjects

stances, reflect diffuse damage to the myocardium of the right ventricle.

The initial portions of the QRS sÊ-loops from 3 subjects with no evidence of cardiac enlargement were similar to those of normal subjects. The late portions of the vectorcardiogram, representing spread of the wave of activation through the right ventricle, were smooth in contour. None exhibited the extensive irregularities encountered in some of the subjects with ventricular disease.

The small number of subjects in the last two groups studied does not permit establishment of any conclusions. However, it appears that further studies of this type are indicated, since aids to the diagnosis of right ventricular hypertrophy in the presence of right bundle branch block and recognition of right bundle branch block without associated myocardial disease would be of considerable clinical value.

The QRS sÊ-loops of the subjects with left ventricular hypertrophy and right bundle branch block exhibited considerable similarity, suggesting that it may be possible to recognize this combination of lesions by spatial vectorcardiograms.

Records obtained from small groups of subjects with isolated right ventricular hypertrophy and right bundle branch block and with right bundle branch block not associated with cardiac enlargement seemed to have some distinctive features and indicate the desirability of further study of the spatial vectorcardiogram in these states.

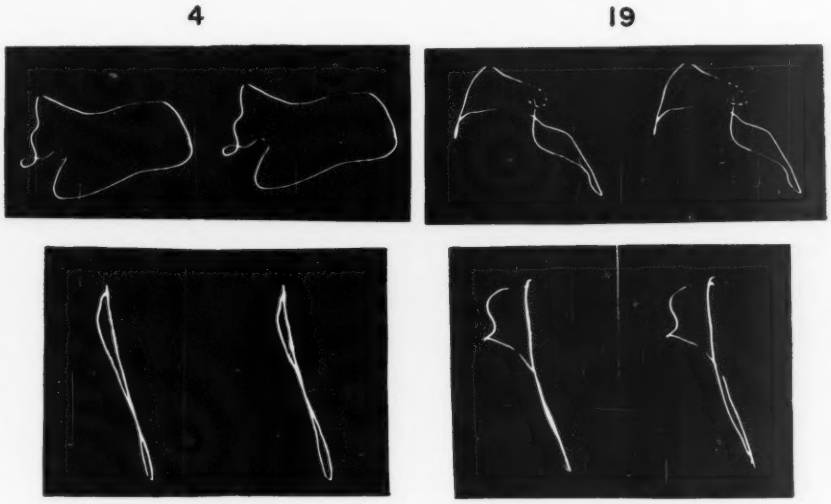


FIG. 5. Stereoscopic photographs of wire models representing QRS sÊ-loops of the representative subjects whose electrocardiograms are shown in figure 4. Stereoscopic effects are best obtained from these photographs by placing a card between the respective pairs and viewing them from a distance of 5 to 10 inches.

SUMMARY

The QRS sÊ-loops of 24 subjects with electrocardiographic evidence of right bundle branch block have been described. The records have been divided into three groups, on the basis of clinical and roentgenographic evidence of ventricular hypertrophy.

REFERENCES

[1] CONWAY, J. P., CRONVICH, J. A., AND BURCH, G. E.: Observations on the spatial vectorcardiogram in man. Am. Heart J. **38:** 537, 1949.

[2] PANTRIDGE, J. F., ABILDSKOV, J. A., BURCH, G. E., AND CRONVICH, J. A.: A study of the spatial vectorcardiogram in left bundle branch block. Circulation **1:** 893, 1950.

[3] CRONVICH, J. A., ABILDSKOV, J. A., JACKSON, C. E., AND BURCH, G. E.: An approximate derivation for stereoscopic vectorcardiograms with the equilateral tetrahedron. Circulation **2:** 126, 1950.

[4] ASHMAN, R. AND BYER, E.: The normal human ventricular gradient. I. Factors which affect its direction and its relation to the mean QRS axis. Am. Heart J. **25:** 16, 1943.

CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

Angiography

By CHARLES T. DOTTER, M.D., ISRAEL STEINBERG, M.D., AND ROBERT P. BALL, M.D.

THE TECHNICS of radiologic examination of vascular structures which will be described constitute outlines of current practices at The New York Hospital-Cornell Medical Center, and may be varied as indicated. The term angiography signifies registration of the outline of a vessel on photographic media through the use of radiant energy. The practical source of radiant energy for this purpose is x-ray. Since there is often only a slight difference in density between blood vessels and surrounding structures, it is necessary to accentuate this difference by the introduction of a substance of greater or lesser radiopacity. Through the use of radiopaque substances, almost the entire vascular system can be explored.

Angiographic examinations, in common with most roentgenographic procedures, are performed regionally due to the limitations of film size, physical factors concerned with the source of roentgen rays and the location of the abnormality being studied. For purposes of classification, the general subject of angiography may be divided into four regional categories; namely, (1) the head, (2) the chest, (3) the abdomen and (4) the extremities. Appropriate subdivisions are utilized to distinguish between the specific structures studied such as veins (venography), arteries (arteriography, aortography) or cardiac chambers and thoracic great vessels (angiocardiography). The present discussion concerns extremity and abdominal angiography; subsequent articles will include angiocardiography and cerebral angiography including dural sinus venography.

From the Department of Radiology of The New York Hospital-Cornell Medical Center, New York, N. Y.

This study was aided by grants from the Schering Corporation and the New York Heart Association.

ANGIOGRAPHIC TECHNIC AND EQUIPMENT IN GENERAL

In angiography, as in any technical procedure, individual preference may be exercised in the selection of apparatus and details of technic. Although apparently trivial details may be crucial, an understanding of the basic purpose of the examination will frequently allow a wide latitude of method. Angiography in any form should not be employed indiscriminately since the intravenous use of the commonly employed contrast media is potentially injurious or even lethal.

An angiographic procedure, to be effective, must take the physiology of the circulation into account. The rate of venous flow is slow compared with arterial flow, which is approximately 50 cm. per second. Timing of exposures is therefore more critical during arteriography than during venography. If more than three seconds is required to complete an intra-arterial injection, a film exposed thereafter will catch only part of the contrast substance, the initially injected portion having already left the arteries. If the exposure is delayed, the result will be the same. Consequently, the rapid introduction of contrast agents into vascular lumens requires adequately sized needles, cannulas or catheters. It is often highly desirable to make serial, rapid roentgenograms of the area during passage of

contrast substance. This is exemplified in angiocardiography and cerebral angiography where a single exposure, no matter how well timed, will not provide the information to be gained from serial study. This may be achieved through such technical advances as automatically operated x-ray roll-film magazines. The Fairchild roll-film cassette affords serial radiography at a rate of two exposures per second.[1] Most modern x-ray tubes and generators have the capacity to meet the needs of angiography.

Contrast Substances for Angiography

The most suitable contrast mediums for angiography consist of an iodine-containing organic molecule in watery solution. In the United States, Diodrast and Neo-iopax are commonly used. Such substances may not be injected without danger.[2, 3] Sensitivity tests have not proved successful in foretelling catastrophes. The organic iodides may be injected into veins in dilute (20 to 40 per cent) or concentrated (70 to 75 per cent) strength. The injection is usually painless. Spasms and pain may follow injection into arteries, particularly when extravasation occurs. Thrombosis may follow intravenous injections, rarely after intra-arterial injections. Other contrast agents include Thorotrast (thorium dioxide) and sodium iodide. The former possesses undesirable radioactive properties and causes painful scar formation if extravasated. Sodium iodide in concentrated solution shows some tendency to cause thrombosis of the injected vessel and has caused death due to mesenteric thrombosis following abdominal arteriography. It is also undesirable in that it ionizes readily in the bloodstream and gives rise to acute iodism. It is apparent that the ideal contrast agent remains to be developed.

Extremities

Veins of the Extremities (Peripheral Venography)

Venography in the living patient was apparently first performed by Berberich and Hirsch[4] in 1923. Notable among review articles are those of Camp and Allen,[5] Allen, Barker and Hines,[6] Barker and Camp,[7] Baker and Miller,[8] Bauer[9] and Edwards.[10]

Technic. A variety of technics have been used with success. Allen and Barker[11] illustrate convincingly that good visualization of veins may be obtained following intra-arterial injection of contrast agents. While the method has the advantage of demonstrating most of the veins of the extremity at the same time, it is more difficult to perform because of dilution of contrast substance and necessity for accurate timing.

The method of venography, which has been most widely employed in the extremities, consists of the direct injection of a contrast substance into a vein distal to the area under investigation with radiographic examination of the extremity at or near the termination of the injection. In study of the veins of the lower extremity, some modification of the following technic will usually suffice:

The patient lies supine on the x-ray table, films in place beneath the leg and thigh which are in slight internal rotation.[21] Under local anesthesia a 16 to 20 gage needle is inserted percutaneously (or after a cut-down) into an ankle vein, preferably the medial malleolar vein. Through this needle 20 to 40 cc. of contrast substance are injected during a period of from 10 to 20 seconds and x-ray exposure is made at or just before the termination of the injection (fig. 1). A tourniquet lightly placed about the leg at the knee is said to obstruct the superficial veins and result in enhanced filling of the deep circulation. Caution is to be exercised in the interpretation of resultant films. If the deep veins are demonstrated, they are patent; the converse is not always true. Study of the competency of the valves of the femoral and saphenous veins is best accomplished by the method of Bauer[9] wherein 10 or more cc. of contrast substance are injected directly into the femoral vein near the inguinal ligament with the patient in a semi-erect posture. An anteroposterior film of the thigh is exposed at the end of the injection (fig. 2).

Venography in the arms differs from that in the legs only in that rapid injections probably are preferable. The injection method described for angiocardiography[12] usually results in excellent demonstration of the veins of the upper arm and shoulder girdle. Through a 12 gage needle inserted into an antecubital or wrist vein, 30 to 40 cc. of dilute contrast substance

are injected as rapidly as possible (in one to two seconds) and a film of the desired region is exposed at the end of the injection. Retrograde filling of the veins of the upper or lower extremity may be achieved with the aid of tourniquets but does not provide physiologic information and may be misleading from an anatomic point of view.

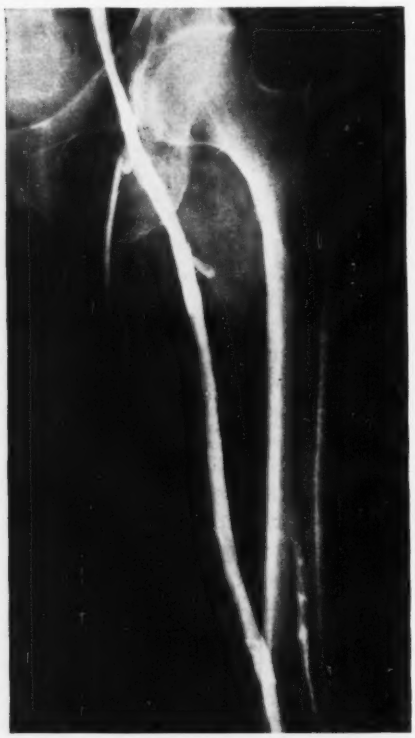


FIG. 1. *Normal Veins, Thigh (Direct Venogram).* 52 year old male (N.Y.H. 558 586). Roentgenogram made at the termination of a ten second injection of 40 cc. Neo-iopax, 37.5 per cent, into the left medial malleolar vein. The saphenous and femoral veins are well filled and normal. Slow injections of 30 to 40 seconds duration may result in passage of much of the contrast substance out of the area of study before the exposure is made.

Due to the relatively slow rate of blood flow in veins, it is usually not necessary to employ multiple exposure technics for venography although it may be desirable to obtain stereoscopic or two-projection studies in certain instances. Venography is usually painless but local discomfort follows the extravasation of contrast substance and thrombosis of the injected vein occasionally follows the examination.

Clinical Applications. In general, venography of the lower extremity is concerned with the problems of varicose veins, obstruction, thrombophlebitis and generalized vascular diseases which affect the veins of the leg. Venography of the upper extremity is usually performed in an effort to identify a cause for clinically apparent venous obstruction.

FIG. 2. *Incompetent Femoral Vein Valves (Venogram, Bauer Technic).* 46 year old male with bilateral varicose veins (P.H. 224 674). Film made following the injection of 15 cc. dilute contrast substance into the left femoral vein at the inguinal ligament, patient in a semi-erect position. Incompetence or absence of femoral vein valves has caused a reversal in the direction of femoral vein flow resulting in varicose veins.

Venographic examination of the leg is most often used in connection with the surgical treat-

ment of varicose veins. The surgeon desires to know whether or not the deep venous circulation is patent before he ligates and strips the superficial channels. This information is usually obtainable by injection of contrast substance into an ankle vein as described above. The surgeon is usually interested also in knowing whether or not the valves in the deep veins of the thigh are competent. If the femoral valves are incompetent or absent, varices are not likely to be cured by saphenous ligation. This is particularly pertinent in the investigation of varicosities in the young adult.[13] By injecting the radiopaque solution directly into the femoral vein with the patient in the semi-erect position,[9] the question may be answered. If the valves are incompetent, the injected media will be seen to flow peripherally (fig. 2).

Direct venography provides an excellent means for the demonstration of venous blocks.[7] These are particularly common about the shoulder girdle.[14] Films show the site of block and demonstrate the collateral channels which develop in response to the obstruction. Caution should be exercised in interpreting the films, since various causes such as tumor, thrombosis or the scalenus anticus syndrome (fig. 3) may produce strikingly similar angiographic findings.

Angiography of the veins, particularly in the lower extremities, has supplied anatomic information in the study of a variety of other disorders. These include thromboembolic diseases,[9, 15, 16] thromboangiitis obliterans[17] and vasomotor trophic disturbances.[16, 18, 19] Known pitfalls in venographic interpretation exist[20]; interpretation should be based upon a knowledge of the anatomy concerned.[21, 22]

Arteries of the Extremities (Peripheral Arteriography)

Due to the accessibility of peripheral arteries the injection of contrast substance into their lumens is usually not difficult. The direction and nature of arterial blood flow facilitates the investigation, carrying contrast substance into all functional arteries distal to the site of injection. Arteriography, using sodium bromide, was performed in man in 1923[4] and the use of sodium iodide was described by Brooks in 1924.[23] Review articles on the subject of peripheral arteriography include those of Camp and Allen,[5] Kleinsasser,[24] Jones and Steiner[25] and Edwards.[10]

Technic. Arteriography of the extremities may be conducted by two somewhat different methods, direct and retrograde. In the direct method, which is the most widely employed, an 18 to 22 gage needle is inserted into an accessible artery proximal to the desired site of study, the needle being pointed in the direction of blood flow. Local anesthesia is usually employed and occasionally surgical exposure of the artery is carried out. A 10 to 15 cc. dose of dilute contrast solution is then injected as rapidly as possible (in one to three seconds) and x-ray exposure of the extremity conducted at the instant the injection is complete (fig. 4). Accurate timing is imperative since contrast substance leaves the arteries with great rapidity. To slow the passage of the radiopaque medium through the vessels, partial or complete occlusion of the artery proximal to the

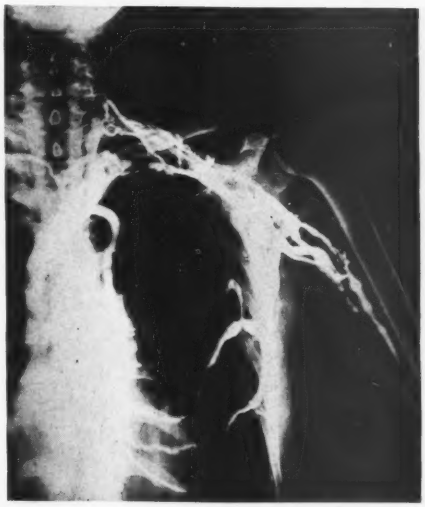


FIG. 3. *Scalenus Anticus Syndrome (Direct Venogram, Angiocardiographic Technic).* 33 year old female (N.Y.H. 527 262) with pain and limitation of motion at the left shoulder of four years' duration. Roentgenogram exposed at termination of one and one half second injection of 32 cc. of Neo-iopax into median basilic vein through a 12 gage needle. Symptoms responded dramatically to surgical severance of the anterior scalene muscle.

point of injection may be accomplished by the use of digital compression, tourniquets or a sphygmomanometer cuff.[25] Rapid serial roentgenographic methods have greatly simplified the problem of arteriography, minimizing the need for precise timing or the artificial de-

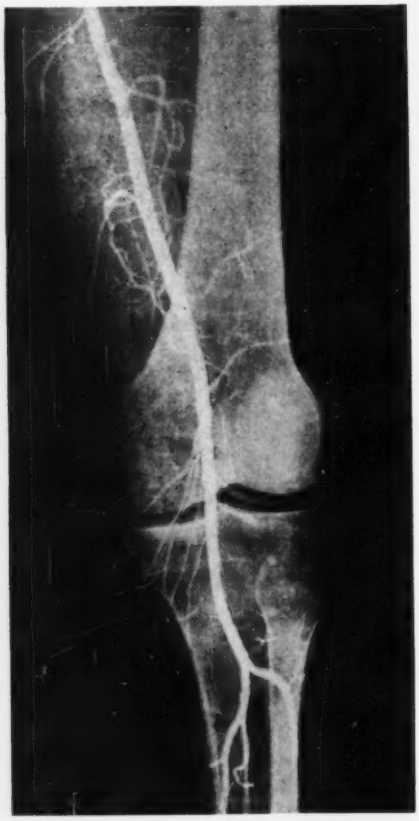


FIG. 4. *Normal Arteries, Leg (Direct Peripheral Arteriogram).* 41 year old male with extensive varices of left leg (N. Y. H. 128 503). Roentgenogram exposed at termination of two second injection of 30 cc. of Diodrast, 35 per cent, into the femoral artery at the inguinal region. Femoral, popliteal, geniculate, anterior tibial, peroneal and posterior tibial arteries sharply outlined.

celeration of arterial flow. Serial exposures are made during the entire period of injection and for a few seconds thereafter at a rate of one or more exposures per second. The physiologic and anatomic status of the arterial and venous circulation may thus be studied with one injection.

Retrograde arteriography of the extremities[27] is accomplished by the forcible injection of contrast substance into an artery, distal to the area under examination. The artery is usually occluded below the site of injection and the radiopaque solution is driven in retrograde fashion back along the lumen of the injected vessel. This technic is of particular value in the examination of the axillary and subclavian arteries. A similar method consists of catheterization of the artery by polyethylene tubing introduced through a small cut in the surgically exposed vessel. The tubing is advanced until its tip lies close to the desired area of study and the injection carried out (fig. 5).

Clinical Applications. Arteriography of the extremities is useful in the study of arteriovenous fistulas and aneurysms, obliterative arterial disease, arterial emboli, arterial injuries and their surgical repair, and malignant bone tumors.

Congenital or acquired arteriovenous communications are best studied by arteriography. If the lesion to be studied is in the distal portion of the arm or leg, injection is made into the artery proximal to the lesion. When the lesion lies centrally, retrograde injection is the more effective technic (fig. 5). It is virtually a surgical necessity to delineate the arterial feeders of both the congenital and acquired lesion prior to operation. Congenital lesions are often complex intercommunications between arteries and veins and cannot be surgically corrected unless all the communicating vessels are interrupted.

Arteriography aids in the localization of arterial emboli prior to embolectomy. It demonstrates the site of arterial injuries and provides a means for the evaluation of the adequacy of surgical repair. The location, type and degree of obliterative arterial disease such as arteriosclerosis obliterans or thromboangiitis obliterans can be assessed by arteriography. A study of the vascular pattern associated with malignant bone tumors has provided an additional method for differential diagnosis.[24] Giant cell tumors, for example, show vascularity around their periphery, while malignant bone tumors usually show irregular pooling of contrast substance within the tumor. The information available is comparable to that obtained by cerebral

angiography in the study of brain tumors and direct nephrography in the study of renal tumors.

and Caldas,[27] the technic, indications and findings have been summarized by Nelson[28] and Wagner.[29]

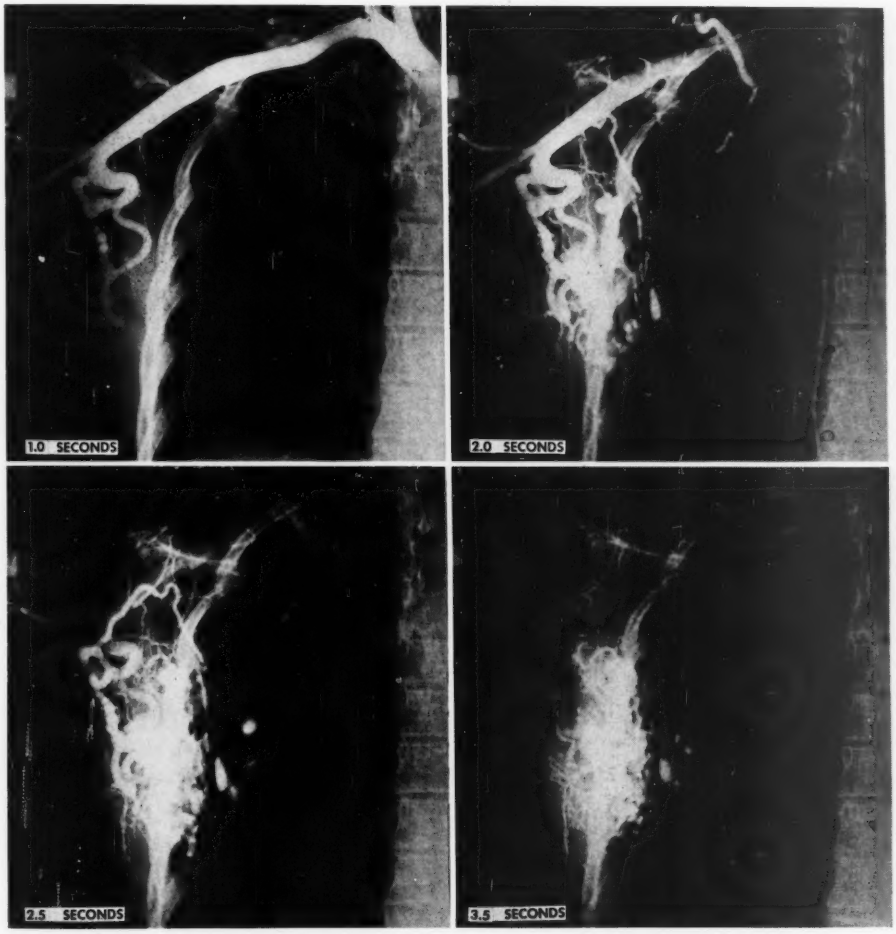


FIG. 5. *Congenital Arteriovenous Fistula, Right Scapula (Retrograde Peripheral Arteriogram).* 22 year old female (N.Y.H. 572 681). Polyethylene tubing inserted into brachial artery at antecubital fossa and passed proximally for five inches. Forty-five cc. of 75 per cent Neo-iopax were injected during one second, roentgen exposures being made every half second during and for 10 seconds following the injection. Films selected from series show complex arteriovenous fistula filling from numerous arteries arising from axillary, subclavian and transverse scapular arteries. Delineation of lesions facilitates surgical treatment.

ABDOMEN

Arteries of the Abdomen (Abdominal Aortography)

Abdominal aortography as employed in this country makes use of the injection of contrast substance directly into the abdominal aorta. Originally described by Dos Santos, Lamas

Technic. The patient is placed face-down upon an x-ray table and a general anesthetic (usually intravenous Pentothal) administered. A 15 cm. long, 18 gage needle with a stylet is then inserted directly into the aorta, skin puncture being made below the twelfth rib and about 5 cm. to the left of the spinous process.

When the needle enters the aorta the stylet is removed and, following a trial injection of saline, a syringe containing 10 to 15 cc. of contrast substance attached. A single bucky film of the abdomen is exposed at the end of the injection, which takes about two or three seconds. Neo-iopax, 75 per cent, or Diodrast, 70 per cent, may be employed as contrast mediums. Sodium iodide, 80 per cent, also used for this procedure, is slightly more radiopaque than Neo-iopax or Diodrast but has the disadvantage of causing acute iodism if

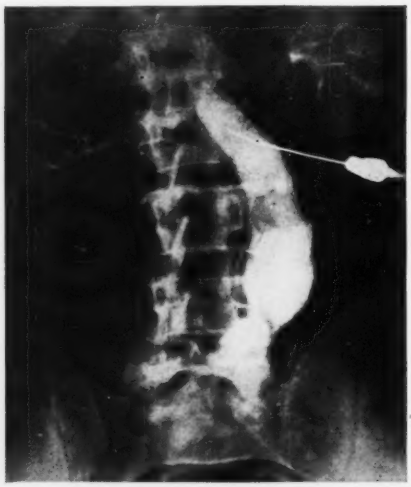


FIG. 6. *Arteriosclerotic Aneurysm of Abdominal Aorta (Translumbar Abdominal Aortogram).* 62 year old male (P.H. 379 578). Posteroanterior film of abdomen made following rapid injection of 10 cc. of 80 per cent sodium iodide through an 18 gage needle inserted into aorta posteriorly. Patient under general anesthesia. A fusiform aneurysm of the aorta is outlined.

the injection is repeated. Utilizing a pressure injection apparatus and a 14 gage needle introduced into the aorta as described above, Milanes and co-workers[32] have been able to inject up to 50 cc. of concentrated Diodone within a total period of one and one-half seconds. Their films are striking. Visualizati n of the abdominal aorta may also be accomplished by forcible retrograde injection through a femoral artery[28] or following catheterization of the aorta from below.[31] Both of these methods lack the ease and simplicity of translumbar puncture. Abdominal or translumbar aortography has resulted in death due to mesenteric artery thrombosis and should not be used for purely academic purposes.

Clinical Applications. Contrast visualization of the abdominal aorta has proved useful in the delineation of abdominal aortic aneurysm (fig. 6) and in the differentiation of this lesion from clinically similar para-aortic tumor mas-

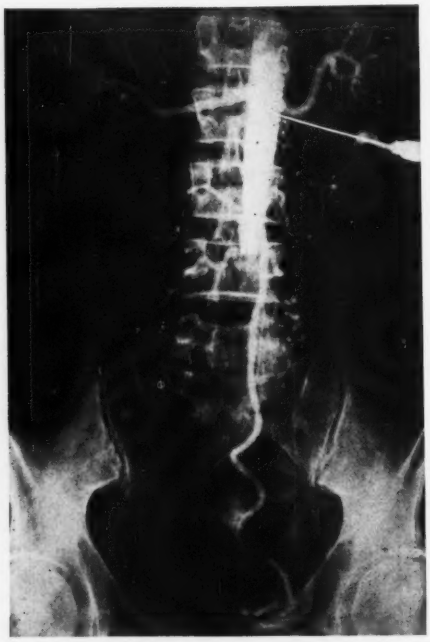


FIG. 7. *Thrombotic Obliteration of the Aortic Bifurcation—Leriche Syndrome (Translumbar Abdominal Aortogram).* 48 year old male with intermittent claudication (N.Y.H. 315 795). Film exposed following two to three second injection of 20 cc. of 70 per cent Diodrast through an 18 gage needle inserted via translumbar route. Obstruction and collateral channels are outlined as are the renal arteries.

ses. Blakemore[33] has made use of the method in evaluating the results of wiring procedures for the correction of aneurysm. Aneurysms of the iliac, renal and splenic arteries are accessible to study by this method.

Occlusion of the abdominal aorta or its branches is clearly demonstrated by aortography (fig. 7) and the extent of collateral circulation revealed.[34,35] Saddle emboli may be

localized. Intra-abdominal tumors may be studied by visualization of their vascular supply while malignancy is suggested by pooling of contrast substance within the tumor. Hartnet has used abdominal aortography to visualize the human placenta.[36]

Abdominal aortography has aided in the differential diagnosis of renal tumors.[37] Renal carcinomas show an irregular, mottled pooling of contrast substance while renal cysts are usually not demonstrably vascular. Since papillary carcinoma of the renal pelvis also fails to show pooling, the absolute diagnosis of benign cyst should probably not be made. Anomalies in the course of the renal arteries are demonstrable by this method as are the abnormal vascular patterns associated with horseshoe and ectopic kidneys.[38] Opacification of the parenchyma of kidneys and spleen can usually be obtained if desired and may aid in the identification of abdominal masses.

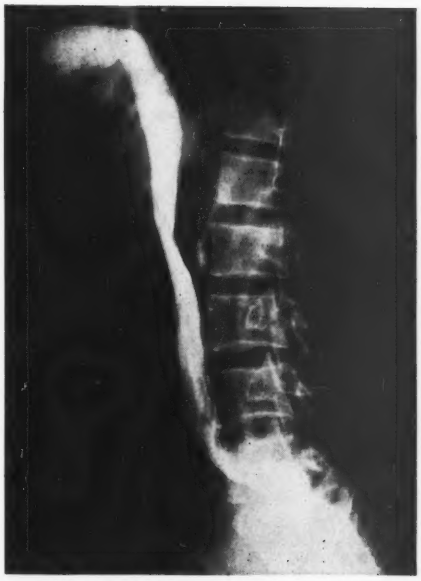


FIG. 8. *Normal Inferior Vena Cava (Abdominal Venogram)*. 45 year old male (N.Y.H. 383 773). Lateral film of abdomen made four seconds following the beginning of a rapid (two second) injection of 45 cc. of Diodrast into the left medial malleolar vein.

Veins of the Abdomen

Several technics are available for study of intra-abdominal veins. The iliac veins and the inferior vena cava are easily studied angiographically. Castellanos and Pereiras[39] and Farinas[40] advocated the insertion of a trocar into the saphenous or femoral vein through which a dose of 30 to 40 cc. of contrast substance was injected and roentgen exposure made at the end of the injection. The technic should be similar to that used during angiocardiography. Unnecessary cut-down upon the saphenous or femoral vein is avoided by inserting the large bore needle into a malleolar vein. The patient is studied in the head-down (Trendelenburg) position and the roentgen exposure made two to four seconds after the beginning of a two-second injection of 50 cc. of contrast substance (fig. 8). The technic is chiefly of value in the demonstration of thrombotic or neoplastic occlusion of the inferior vena cava or iliac veins.

The cardiac catheter may regularly be positioned in certain of the tributaries of the inferior vena cava, notably the hepatic and renal veins. Forcible injection of 25 to 30 cc. of contrast substance through the catheter is immediately followed by roentgen exposure of the abdomen (fig. 9). The cardiac catheter can be manipulated so as to traverse a portocaval anastomosis, subsequent injection outlining the

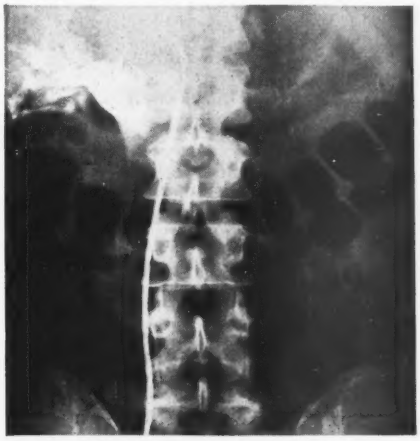


FIG. 9. *Normal Right Renal Veins (Cardiac Catheter Study)*. 40 year old male (N.Y.H. 315 779). Film exposed at termination of a five second injection of 30 cc. of 70 per cent Diodrast through catheter tip in right renal vein.

portal vein and proving patency of the anastomosis.[41] The biochemical investigations made possible by catheterization of the portal vein in this manner undoubtedly are of greater potential value than angiographic studies. A new aid to surgery of the pancreas and portal vein has been described by Child.[42] At the time of exploration prior to anticipated resection of the pancreas for malignant disease it is of great value to ascertain the extent to which the portal vein has been involved by tumor. Portal venography is accomplished by the rapid

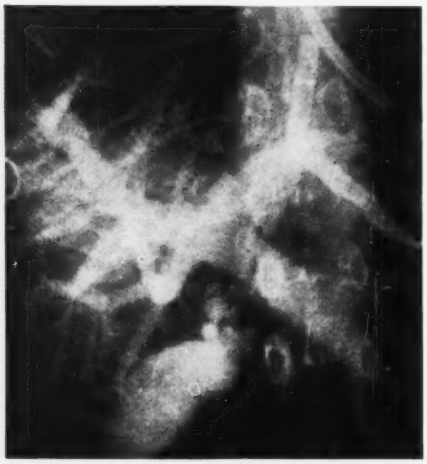


FIG. 10. *Normal Portal Vein (Portal Venogram At Laparotomy).* 37 year old female (N.Y.H. 584 105). Thirty cc. of 35 per cent Diodrast rapidly injected through an 18 gage needle positioned in branch of superior mesenteric vein. The portal vein and its intrahepatic radicles are normal. (There is opaque medium in the gall bladder following cholangiography.)

injection of dilute Diodrast into a tributary of the portal vein. The injection lasts about 10 to 15 seconds and is followed immediately by roentgen examination of the abdomen (fig. 10). Further experience with portal venography is expected to define its usefulness in detecting hepatic metastases and demonstrating vascular changes in a variety of hepatic diseases.

REFERENCES

[1] DOTTER, C. T., STEINBERG, I., AND TEMPLE, H. L.: Automatic roentgen-ray roll-film magazine for angiocardiography and cerebral arteriography. Am. J. Roentgenol. **62:** 355, 1949.

[2] PENDERGRASS, E. P., CHAMBERLIN, G. W., GODFREY, E. W., AND BURDICK, E. D.: Survey of deaths and unfavorable sequelae following the administration of contrast media. Am. J. Roentgenol. **48:** 741, 1942.

[3] DOTTER, C. T., AND JACKSON, F. S.: Death following angiocardiography. Radiology **54:** 527, 1950.

[4] BERBERICH, J., AND HIRSCH, S.: Die röntgenographische Darstellung der Arterien und Venen am lebenden Menschen. Klin. Wchnsch. **2:** 2226, 1923.

[5] CAMP, J. D., AND ALLEN, E. V.: Angiography. In Golden, Ross: Diagnostic Roentgenology. New York, Thomas Nelson and Sons, 1941. Vol. 2, Ch. 18, pp. 1143–1168.

[6] ALLEN, E. V., BARKER, N. W., AND HINES, E. A., JR.: Peripheral Vascular Diseases. Philadelphia, W. B. Saunders Company, 1946. P. 871.

[7] BARKER, N. W., AND CAMP, J. D.: Direct venography in obstructive lesions of the veins. Am. J. Roentgenol. **35:** 485, 1936.

[8] BAKER, E. C., AND MILLER, F. A.: Further experiences with venography. Radiology **43:** 129, 1944.

[9] BAUER, G.: A venographic study of thromboembolic problems. Acta chir. Scandinav. Suppl. 61, 1940.

[10] EDWARDS, E. A.: The status of vasography. New England J. Med. **209:** 1337, 1933.

[11] ALLEN, E. V., AND BARKER, N. W.: Roentgenologic visualization of the veins of the extremities: Preliminary description of a method. Proc. Staff Meet., Mayo Clin. **9:** 71, 1934.

[12] ROBB, G. P., AND STEINBERG, I.: Visualization of the chambers of the heart, the pulmonary circulation, and the great blood vessels in man. A practical method. Am. J. Roentgenol. **41:** 1, 1939.

[13] CURTIS, A. C., AND HELMS, R. W.: Congenital absence of valves in the veins as a cause of varicosities. Arch. Dermatol. & Syph. **55:** 601, 1947.

[14] HUGHES, E. S. R.: Venous obstruction in the upper extremity (Paget-Schroetter's syndrome). A review of 320 cases. Surg. Gynec. and Obst. **88:** 89, 1949.

[15] DEBAKEY, M., SCHROEDER, G. F., AND OCHSNER, A.: Significance of phlebography in phlebothrombosis. J. A. M. A. **123:** 738, 1943.

[16] BAKER, E. C.: Clinical and roentgenologic evaluation of venography based on 1,027 cases. Am. J. Roentgenol. **58:** 603, 1947.

[17] BROWN, G. E., ALLEN, E. V., AND MAHORNOER, H. R.: Thromboangitis obliterans. Philadelphia, W. B. Saunders Company, 1928. P. 199.

[18] LESSER, A., AND DANELIUS, G.: Venography: Its value in the diagnosis and management of venous disturbances of the lower extremities. Ann. Surg. **119:** 903, 1944.

[19] Brooks, B., and Jostes, F. A.: A clinical study of diseases of the circulation of the extremities. Description of a new method of examination. Arch. Surg. **9:** 485, 1924.

[20] Epstein, B. S., Wasch, M. G., and Loewe, L.: Angiography. Am. J. Roentgenol. **60:** 650, 1948.

[21] Felder, D. A.: Anatomical-spatial relationships of the deep veins of the lower extremity as a basis for venographic interpretation. Radiology **54:** 521, 1950.

[22] Edwards, E. A., and Roback, J. D., Jr.: Applied anatomy of the femoral vein and its tributaries. Surg. Gynec. & Obst. **85:** 547, 1947.

[23] Brooks, B.: Intra-arterial injection of sodium iodide. J. A. M. A. **87:** 1016, 1924.

[24] Kleinsasser, L. J.: Peripheral arteriography. Surgery **22:** 930, 1947.

[25] Jones, C., and Steiner, R. E.: Investigation and treatment of arterial disturbances in the lower limbs. Brit. J. Surg. **36:** 286, 1949.

[26] Allen, E. V., and Camp, J. D.: Arteriography: a roentgenographic study of the peripheral arteries of the living subject following their injection with a radiopaque substance. J. A. M. A. **104:** 618, 1935.

[27] Freeman, N. E., and Miller, E. R.: Retrograde aortography in the diagnosis of cardiovascular lesions. I. Visualization of aneurysms and peripheral arteries. Ann. Int. Med. **30:** 330, 1949.

[28] Dos Santos, R., Lamas, A. C., and Caldas, J. P.: Artériographie des membres et de l'aorte abdominale. Paris, Masson et Cie, 1931.

[29] Nelson, O. A.: Arteriography of abdominal organs by aortic injection. Surg., Gynec. & Obst. **74:** 655, 1942.

[30] Wagner, F. B., Price, A. H., and Sevenson, F. C.: Abdominal arteriography; technic and diagnostic application. Am. J. Roentgenol. **58:** 591, 1947.

[31] Farinas, P. L.: Retrograde abdominal aortography. Radiology **47:** 344, 1946.

[32] Milanes, B., Perez-Stable, E., Casanova, R., and Bustamante, R.: Estudio radiologico de la aorta abdominal y sus ramos. Rev. cubana de Cardiol. **11:** 109, 1950.

[33] Blakemore, A. H.: Angiography—an evaluation of its usefullness. S. Clin. North America **26:** 326, 1946.

[34] Ortner, A. B.: Abdominal aortography. South. Surgeon **16:** 157, 1950.

[35] Leriche, R., Kunlin, J., and Boely, C.: Lessons of aortography. Angiology **1:** 109, 1950.

[36] Hartnett, L. J.: Arterial visualization in the diagnosis of placenta previa. Am. J. Obst. & Gynec. **55:** 940, 1946.

[37] Nelson, O. A.: Arteriography in renal and abdominal conditions. J. Urol. **53:** 521, 1945.

[38] Wagner, F. B.: Arteriography in renal diagnosis: preliminary report and critical evaluation. J. Urol. **56:** 625, 1946.

[39] Castellanos, A., and Pereiras, R.: La cavografia inferior. Arch. d. med. Int. **4:** 362, 1938.

[40] Farinas, P. L.: Abdominal venography. Am. J. Roentgenol. **58:** 599, 1947.

[41] Dotter, C. T., Payne, M. A., and O'Sullivan, W.: Catheterization of the portal vein in man following portocaval anastomosis. Ann. Surg. **132:** 310, 1950.

[42] Child, C. G., Milnes, R. F., Holswade, G. R., and Gore, A. L.: Sudden and complete occlusion of the portal vein in the Macaca Mulatta monkey. Ann. Surg. **132:** 475, 1950.

ABSTRACTS

BLOOD COAGULATION

Conley, C. L., Hartmann, T. C., and Lalley, J. S.: The Effect of Human Plasma on the Anticoagulant Activity of Heparin. J. Clin. Investigation **29:** 470 (April), 1950.

In this study an effort was made to determine whether or not plasma contains a substance or substances which inactivate heparin. When normal human platelet-deficient plasma was incubated with heparin, there was no detectable alteration in the anticoagulant activity of the heparin. Furthermore, plasma from patients with thrombotic disease had no demonstrable heparin-neutralizing activity. There was no evidence of a "heparinase" present in human plasma.

WAIFE

Losner, S., Volk, B. W., Jacobi, M., and Newhouse, S.: Photoelectric Determination of Prothrombin Time. J. Lab. & Clin. Med. **36:** 73 (Sept.), 1950.

A photoelectric technic was applied in the determination of prothrombin time according to the one stage Quick method. The determinations were easy and accurate, and eliminated the errors made by the naked eye. This method proved to be of particular value in patients with a prolonged prothrombin time placed on anticoagulant therapy. In this latter group with prolonged prothrombin times, the end point is difficult to determine by the Quick method. The results compared favorably with those obtained by the original technic. The mean of 704 determinations by the photoelectric method was 0.65 second lower than that obtained from the same number of determinations by the original technic. The standard deviation for these patients, including 12 dicumarolized patients, was 0.29 second by the photoelectric method as compared to 0.93 second by the original method. A graphic picture was obtained by coupling the photoelectric cell of the Coleman spectrophotometer with the first lead of an electrocardiograph. The curve produced was caused by the increasing density and decreasing transmission of light at the moment of clotting.

MINTZ

CONGENITAL ANOMALIES

Bayer, O. and Landen, H. C.: Contribution to the Diagnosis of Patent Ductus Arteriosus. Schweiz. med. Wchnschr. **80:** 261 (March), 1950.

The authors describe the classic signs of patent ductus arteriosus. They also show that the intensity of the continuous "machinery murmur" diminishes during a Valsalva experiment. Sometimes the murmur disappears almost completely. During the same experiment the bulging of the outflow tract of the right ventricle vanishes and reappears as soon as the experiment stops. Vital capacity, pulmonary ventilation and oxygen consumption per minute were studied in 5 cases before and after the ligation of the ductus. Vital capacity was slightly diminished; pulmonary ventilation and oxygen consumption were increased. These values returned to normal after ligation.

RITTER

Rossi, E., Grob, M., and Gutewa, J.: Pre and Postoperative Capillary Microscopy in Congenital Heart Disease. Helvet. paediat. acta **5:** 279 (June), 1950.

The nailfold capillaries of 51 patients with cyanotic and noncyanotic heart disease were examined. In some cases the studies were carried out before and after surgical treatment. In cyanotic congenital heart disease, the importance of the capillary changes were grossly proportional to the intensity of the cyanosis. The capillary loops were increased in number, elongated, tortuous, and their venous part was dilated. The most pronounced changes were observed in Fallot's tetralogy. They disappeared partly after surgical treatment (Blalock-Taussig operation). The capillaries in noncyanotic congenital heart disease were not significantly altered. The capillary loops in one case of aortic stenosis showed spastic changes, which disappeared completely after surgical correction.

RITTER

Donzelot, E., Durand, M., Melianu, C., and Vlad, P.: Normal Electrical Axis or Deviation of the Axis to the Left in Cyanotic Congenital Heart Disease. A Study of 29 Personal Cases from the Standpoint of the Diagnostic Value. Arch. d. mal. du coeur **43**: 577 (July), 1950.

Among 527 electrocardiograms made on patients with cyanotic congenital malformations of the heart, the authors found 22 cases (4 per cent) with left axis deviation and 7 cases (1.3 per cent) with a normal electrical axis. In the former group, most (18) had tricuspid atresia, 1 an infantile type of coarction, 1 partial transposition of the great vessels associated with pulmonary stenosis; in 2 cases no diagnosis was established. In the group without axis deviation there were 3 proved cases of tricuspid atresia, 1 Eisenmenger's complex, 2 cases of tetralogy of Fallot, 1 complicated by a right-sided aorta and the other by an interauricular septal defect, and finally 1 case of pulmonary hemangioma. The authors conclude that an electrocardiogram showing left or no axis deviation, found in a cyanotic case of congenital heart disease, represents an important diagnostic contribution but is not pathognomonic for any certain malformation.

PICK

Morgan, R. H.: Problems of Angiocardiography. Am. J. Roentgenol. **64**: 189 (Aug.), 1950.

The author discusses the evolution in technic, radiation hazards, and the relatively high patient mortality of angiocardiography. To reduce the radiation hazard, the author has devised a vacuum powered automatic injector device which can be controlled without undue exposure. The author reports 6 deaths in about 600 angiocardiographic procedures (1 per cent), 2 patients dying one-half hour after the injection of only 1 cc. of a trial dose. Two of the 6 deaths occurred in cyanotic patients, the sixth apparently resulting from an excessive dose being delivered to the brain because of an anomalous innominate artery. Second injection hazards may be overcome by taking films in two projections simultaneously.

SCHWEDEL

Sokolow, M., and Edgar, A. L.: A Study of the V Leads in Congenital Heart Disease. With Particular Reference to Ventricular Hypertrophy and its Diagnostic Value. Am. Heart J. **40**: 232 (Aug.), 1950.

The authors present electrocardiographic findings in 153 patients with congenital heart disease, of whom 38 were also studied at autopsy. Augmented unipolar limb leads and six precordial leads were recorded in addition to the standard limb leads. Of 39 patients with uncomplicated patent ductus arteriosus, the electrocardiograms of 21 were within normal limits; 17 showed left ventricular hypertrophy; 1 had incomplete right bundle branch block. Right ventricular hypertrophy was not present in any case of uncomplicated patent ductus arteriosus. There was a good correlation between the size of the ductus and the electrocardiogram; all the patients with a ductus over 1 cm. in diameter had electrocardiographic patterns of left ventricular hypertrophy. In coarctation of the aorta (32 patients), right ventricular hypertrophy indicated an associated lesion. In 8 cases of interauricular septal defect, the electrocardiogram revealed right ventricular hypertrophy in 5 and incomplete right bundle branch block in 3. All 40 cases with the tetralogy of Fallot showed right ventricular hypertrophy. In no case of tetralogy of Fallot was the electrocardiogram normal, nor did it show left ventricular hypertrophy. Six cyanotic patients showed left ventricular hypertrophy due to tricuspid atresia with nonfunctioning right ventricle in 3 instances, tetralogy and a large patent ductus arteriosus in 2, and truncus arteriosus and patent ductus arteriosus in 1.

The reliability of the criteria employed in the recognition of right and left ventricular hypertrophy is demonstrated by the complete agreement of the electrocardiographic and pathologic diagnoses of 38 patients on whom autopsies were performed. The V leads employed in this study proved valuable (1) in providing some inference as to the diameter of the patent ductus arteriosus, (2) in suggesting some associated lesion in patent ductus arteriosus or coarctation of the aorta if right ventricular hypertrophy was present, (3) and in ruling out uncomplicated tetralogy of Fallot if left ventricular hypertrophy was present.

HELLERSTEIN

Old, J. W., and Russell, W. O.: Necrotizing Pulmonary Arteritis Occurring with Congenital Heart Disease (Eisenmenger Complex). Am. J. Path. **26**: 789 (Sept.), 1950.

The authors report a case of necrotizing, pulmonary arteritis (periarteritis nodosa) in an 11 year old boy, with patency of the ventricular septum. On

the basis of this congenital defect and a "partial dextrorotation of the aorta," they regard this case as an example of the Eisenmenger complex. There was an associated chronic pericarditis and mitral and aortic valvulitis, in which a rheumatic etiology could not be excluded. The smaller pulmonary arterial branches (1 to 4 mm. in diameter) were acutely thrombosed, and microscopy revealed both chronic and acute granulomatous occlusive disease. The authors postulate the existence of severe pulmonary hypertension, such as has been shown to be constant and predictable in the Eisenmenger complex, in contrast to other types of congenital heart disease. They believe that the lesions in this case were the anatomic expression of a mechanism by which the elevated pulmonary pressure in Eisenmenger's complex is maintained, although they note that such pulmonary arterial disease has not been previously seen in that type of congenital heart disease.

GOULEY

Brecher, G. A., and Opdyke, D. F.: Effect of Normal and Abnormal Respiration on Hemodynamics of Experimental Interatrial Septal Defects. Am. J. Physiol. **162:** 507 (Sept.), 1950.

The interatrial pressure gradient was examined in anesthetized mongrel dogs in which atrial septal defects were artificially created. The influence of normal respiratory excursion and experimentally altered intrathoracic pressures upon the pressure gradient was observed by cannulation of both atriums and subsequent air-tight closure of the chest in layers. During the expiratory pause between normal respirations, a predominant left to right interatrial pressure gradient was found, which measured about one-half the unoperated, normal control values. Normal inspiration diminished the left to right gradient, and in several instances when the initial differential gradient was low, a right to left shunt was observed during atrial systole. Forceful obstructed inspiratory attempts similarly reduced the pressure gradient, and right to left shunt occurred at the height of atrial systole, persisting for at least three atrial cycles. Induced dyspnea was followed by a fall in left atrial pressures, with a reversal of the pressure gradient from right to left for as long as two atrial systolic cycles. Increased intrathoracic pressure did not significantly alter the interatrial pressure gradient. Rapid saline infusions led to right heart failure in the presence of large septal defects, presumably on a basis of the inability of the right ventricle to discharge the load. During heart failure, inspiration magnified the effective right atrial pressure, and right to left shunt was present throughout the entire atrial cycle.

HECHT

Askey, J. M. and Kahler, J. E.: Longevity in Extensive Organic Heart Lesions: A Case of Lutembacher's Syndrome in a Man Aged 72. Ann. Int. Med. **33:** 1031 (Oct.), 1950.

A man of 72, admitted to the hospital because of severe congestive failure, was known to have had auricular fibrillation and intermittent episodes of cardiac decompensation for 15 years prior to his hospitalization. He died six days after admission, and necropsy revealed the presence of an interatrial septal defect, dilatation of the pulmonary artery, and a mitral stenosis (Lutembacher's syndrome). This syndrome had not been suspected during life, presumably because of failure to obtain a chest roentgenogram.

WENDKOS

Olney, M. B., and Stephens, H. B.: Coarctation of the Aorta in Children. J. Pediat. **37:** 639 (Oct.), 1950.

The authors published observations on 14 cases of coarctation of the aorta, 12 of which had surgical repairs. In the 5 youngest patients, whose ages ranged from 4½ months to 4½ years, the reason for hospitalization was cardiac decompensation. The x-ray examination revealed generalized cardiac enlargement with a poorly visualized aortic knob. None showed notching of the ribs. Four electrocardiograms taken showed right ventricular hypertrophy in 3 cases, and a normal axis in 1. Retrograde carotid arteriograms were done in 4 of these 5 youngest patients. Coarctation was demonstrated just distal to the ligamentum arteriosum. There was no evidence of appreciable collateral circulation.

In the group of 9 patients between 4½ and 14 years of age, the presenting symptom was claudication in the lower extremities. Cardiac enlargement on x-ray study was seen in 3 cases, and in 5 there was a small or absent aortic knob. There was notching of the ribs in 4 cases, with the youngest patient showing notching at 6½ years. In retrograde carotid arteriograms the coarctation was seen distal to the ligamentum arteriosum, except in 1 patient where it involved the aorta from the eleventh dorsal vertebra to the first lumbar vertebra. The electrocardiogram was normal in 4 patients and showed left ventricular hypertrophy in 5.

The authors recommend early operation. The complication of aneurysm at the suture line is thought not to develop in end-to-end anastomosis except in the presence of subacute bacterial endocarditis.

MARGOLIES

Parsons, Clifford G.: Cor Triatriatum. Concerning the Nature of an Anomalous Septum in the Left Auricle. Brit. Heart J. **12:** 327 (Oct.), 1950.

The author describes a heart in which an anomalous septum subdivided the left auricle into two chambers. He summarizes other cases previously reported in the literature and examines critically the theories advanced to explain this malformation. He concludes that the most plausible theory is that

which postulates a defect at the junction between the pulmonary veins and the left auricle due to arrested development in the second month of fetal life.

SOLOFF

Denolin, H., Lequime, J., Goksel, F., and Pannier, R.: Tricuspid Atresia. A Clinical and Physiopathologic Study of Two Cases. Acta cardiol. **5:** 400, 1950.

The authors report their observations on 2 adults, 20 and 30 years of age respectively, with cyanosis since early childhood. Both showed left axis deviation in the electrocardiogram. The diagnosis of congenital atresia of the tricuspid valve was substantiated by cardiac catheterization, during which the tip of the catheter failed to enter the right ventricular cavity and in one case was passed through an interatrial septal defect into a pulmonary vein. Angiocardiography in one case revealed simultaneous filling of all cavities of the heart and of the aorta and pulmonary artery. The pulmonary flow at rest was found to be low in both cases, but larger than the systemic flow in the second case. Following exercise, both cases showed increased arterial desaturation and a decrease of the utilization quotient of oxygen. The authors stress the importance of an exercise test for the determination of inadequate pulmonary circulation, especially in the selection of cyanotic patients for a surgical procedure of the Taussig-Blalock type.

PICK

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Mainzer, Fr.: Heart Contusion in Coronary Disease. Cardiologia **16:** 287 (May), 1950.

The author reports 2 cases of contusion of the heart in patients with electrocardiographic evidence of coronary disease. Although the injury was due to a fall on the right side and was slight in both cases, acute cardiac dilatation occurred in the first patient and acute left heart failure with incipient pulmonary edema in the second patient. Recovery was rapid in both patients. It is pointed out that the trauma in these cases should be classified as heart concussion rather than contusion, since there was presumably no direct cardiac impact from the chest wall, but only the displacement of the heart by the effect of gravitation. The disproportion between the trauma and the clinical effect was probably related to the previous coronary disease. The electrocardiographic changes were conspicuous and suggested posterior wall damage in both cases. However, the findings were not suggestive of traumatic coronary thrombosis, although its presence could not be definitely excluded.

SCHWARTZ

Agress, C. M., Rosenburg, M., Schneiderman, A., and Brotman, E. J.: Blood Volume Studies in Shock Resulting from Myocardial Infarction. I. Studies with Evans Blue Dye (T — 1824). J. Clin. Investigation **29:** 1267 (Oct.), 1950.

The blood volume changes in 32 patients with proved acute myocardial infarction are reported. The average blood volume of the 10 cases not in shock was 84 cc. per Kg.; 72 cc. per Kg. in the 10 patients in moderate shock; and 73 cc. per Kg. in the 12 cases that were severely shocked. Blood volume determinations done on surviving patients after convalescence revealed that patients with shock had had a 16 per cent reduction in blood volume.

The use of peripheral venous pressure to distinguish shock from congestive failure could not always be used in studying patients of this type. Venous pressures were not infrequently found to be elevated in severely shocked patients showing extreme vasoconstriction but without evidence of heart failure.

WAIFE

CONGESTIVE HEART FAILURE

Baldwin, D. S., Sirota, J. H., and Villarreal, H.: Diurnal Variations of Renal Function in Congestive Heart Failure. Proc. Soc. Exper. Biol. & Med. **74:** 578 (July), 1950.

Employing a constant intravenous infusion technic, simultaneous endogenous creatinine chromogen, inulin and *p*-aminohippurate clearances were determined during four to six periods throughout 24 hours in 10 male subjects with congestive heart failure. In 6 subjects sodium excretion was also followed. At the time of the study, 6 patients had persistent or increasing peripheral edema in spite of complete bed rest, low salt diet and complete digitalization. Two of the patients were edema free and 2 were undergoing diuresis, spontaneous in one case and the result of digitalis in the other case. With the exception of one individual, mercurial diuretics were withheld for at least five days prior to the study.

Although the number of patients studied was small, certain conclusions appeared to be warranted. In the group with persistent edema, the urine flow either remained constant or increased during sleep, in contradistinction to the decrease in urine flow which occurred in normal subjects. In the same group, the filtration rate increased 6 to 35 per cent during sleep, whereas in normal subjects this function remained the same or decreased. Four subjects with congestive heart failure, who were edema free or undergoing diuresis, showed a diurnal pattern of urine flow and filtration rate similar to that seen in normal subjects. Chloride and sodium excretion decreased in normal subjects during sleep. Two of the three patients with edema showed a marked increase in sodium excretion at night, and 2 other patients showed a slight increase. One edema free patient and 1 patient completely digitalized showed reduced

excretion of sodium at night. The endogenous creatinine chromogen clearance was lower than the inulin clearance in patients with congestive heart failure and edema.

MINTZ

ELECTROCARDIOGRAPHY

Boden, E. and Bayer, O.: Alterations of the Electrocardiogram in Aortic Insufficiency Depending on Blood Pressure and Heart Rate. Contribution to the Question of Coronary Circulation in Aortic Insufficiency. Arch. f. Kreislaufforsch. **16:** 1 (May), 1950.

Inverted T waves in the limb leads and left sided chest leads, present in the electrocardiograms of patients with aortic insufficiency of various etiology, may become upright at the height of an exercise test or following injection of suprarenin. This change in the electrocardiogram can be correlated with the increase of heart rate and the rise of both systolic and diastolic pressure effected by the experiment. In the opinion of the authors the normalization of the T wave indicates a transient improvement of the impaired coronary circulation present in cases of aortic insufficiency. An increase in heart rate, achieved mainly by shortening the diastolic phase of the heart cycle, shortens the time of regurgitation of blood into the ventricle, while an elevation of the mean arterial pressure is associated with an increase of the intra-aortic pressure; both factors have the same tendency to increase the inflow into the coronary system and thus to normalize the electrocardiogram. Persistence of T-wave inversion following exercise in cases of aortic insufficiency suggests organic involvement of the coronary arteries.

PICK

Lepeschkin, E.: Electrocardiographic Observations on the Mechanism of the Electrical Alternans of the Heart. Cardiologia **16:** 278 (May), 1950.

The author presents a detailed electrophysiologic classification of electrical alternans and illustrates some of its less common forms by experimental electrocardiograms. Four main types of electrical alternation of the heart are discussed. The first type, alternation of invasion or of the sequence of activation, is characterized by alternation of QRS accompanied by alternation of S-T and T, equal in area, but opposite in direction. It may be due to alternating delay or complete block of conduction in some portions of the ventricular muscle, or to alternating premature activation of some portions of the ventricular muscle. The second type, alternation of possession or response, is characterized by alternating displacement of the RS-T segment without significant alternation of QRS. The third type, alternation of regression or restitution, is characterized by primary alternation of the T wave and Q-T duration. A fourth type, that of alternation of potential distribution, is due to mechanical alternans. Finally, there may be combinations of the above types of electrical alternans.

SCHWARTZ

Maldonado Allende, I.: Congenital Heart Block. Pregnancy and Heart Block. Rev. argent. de cardiol. **17:** 137 (May, June), 1950.

The author presents clinical data on 6 cases of congenital A-V block. In order to establish such a diagnosis, the following criteria are suggested: electrocardiographic evidence of fetal bradycardia or knowledge that bradycardia was present in early childhood; existence of congenital malformations; good tolerance of normal activities including pregnancies; history of syncopal seizures, usually mild; no history of diseases which may have damaged the myocardium.

All the cases presented were young adults with history of a slow pulse since early childhood. Ventricular septal defect was diagnosed in all cases, while 3 also had extracardiac malformations. Three women tolerated well one, two, and six pregnancies respectively; 2 were successfully operated on. All patients led a normally active life and had no significant complaints. Episodes of dizziness, fainting, or convulsions were recorded in the past history.

Congenital heart block is rare and has a favorable prognosis if no complications are present.

LUISADA

Bill, A. H., Jr., Peirce, E. C., II, and Gross, R. E.: Experimental Production of an Extracardiac Shunt around the Mitral Valve. Arch. Surg. **60:** 1114 (June), 1950.

Experiments have been started in an attempt to circumvent an obstructed mitral valve. The authors describe attempts to construct a pathway from the left auricle to the left ventricle, by-passing the mitral valve, in which a preserved segment of dog aorta is used and fitted with an aortic valve freshly taken from another dog.

From experiments on a series of dogs, the authors reach the following conclusions: (1) The construction of shunts around stenosed valves is possible; (2) a ventricular wall can be penetrated and a vessel attached thereto; (3) the major portion of an extracardiac shunt can probably be constructed from preserved (homologous) vessel grafts; (4) it is impossible to incorporate any valves into the system because of rapid degeneration in the leaflets, leading to regurgitation. The authors further believe that if any such extracardiac shunt is to have permanent value, there must first be developed a successful artificial valve mechanism which could be inserted into the system.

KLOSK

Sandberg, A. A., Scherlis, L., Grishman, A., Master, A. M., and Wener, J.: The Q Wave in Esophageal

Electrocardiography. Am. Heart J. **40:** 47 (July), 1950.

The authors found deep Q waves (0.4 mv. or 20 per cent of R) in tracings obtained from the lower esophagus in 15 patients with posterior myocardial infarction and in normal individuals without evidence of infarction. Lead V_F gave patterns that were essentially similar to the patterns recorded by the lower esophageal electrodes, reflecting the diaphragmatic surface of the heart. Multiple esophageal leads do not appear to aid in the diagnosis of localized posterior wall infarction, especially in the auricular margin, since similar patterns (QS or QR), formerly considered diagnostic, were also observed in patients without infarction.

HELLERSTEIN

Schlachman, M., and Rosenberg, B.: The Effect of Potassium on Inverted T Waves in Organic Heart Disease. Am. Heart J. **40:** 81 (July), 1950.

The authors studied the effect of oral potassium salts (5 to 16 Gm.) on the electrocardiograms of 31 patients with left ventricular hypertrophy or a myocardial infarct. Nine showed significant alterations in the T wave, unrelated to the serum potassium level or to the amount of potassium salt administered. The normalizing effect of potassium on the T wave occurred within 15 minutes and was transient, subsiding completely within two hours. Potassium is considered to produce a functional alteration in the membrane potentials of the myocardium. The response to potassium salts cannot be used to differentiate between inverted T waves which are functional and those due to organic heart disease.

HELLERSTEIN

Soulié, P., Voci, G. and Nichoyanopoulos, J.: The Electrocardiogram of Chronic Constrictive Pericarditis. Arch. d. mal. du coeur **43:** 633 (July), 1950.

On the basis of personal observations of 7 cases of chronic constrictive pericarditis, the authors describe an electrocardiographic pattern which they consider to be typical of the disease. The characteristic changes consist of the presence of sinus rhythm; widened, tall and notched P waves; depression of RS T segment in several limb and precordial leads, associated with flat and inverted T waves in all or most of the leads. Low voltage of the QRS complex is an inconstant finding. The alterations of the P wave may be present in an early stage, before the development of typical clinical signs of the conditions, and are, therefore, of prognostic value. All electrocardiographic anomalies, which are ascribed by the authors to chronic irritation and recurrent inflammation of the pericardium and subepicardium, may disappear following surgical intervention and cardiolysis.

PICK

Soderstrom, N.: What is the Reason for the Ventricular Arrhythmia in Cases of Auricular Fibrillation? Am. Heart J. **40:** 212 (Aug.), 1950.

The author studied the mechanism of the ventricular arrhythmia due to auricular fibrillation by plotting the R-R intervals of 100 consecutive beats on special charts. In 14 of 34 patients studied, the R-R intervals had a distinct tendency to concentrate at certain levels. At rest, R-R intervals ranged from 0.40 to 1.40 seconds, with the majority of beats at the level of 0.65 to 0.70 second. After exercise, there was a distinct concentration of practically all beats at 0.35 second, and the rhythm appeared nearly regular. The return of the ventricular activity to control levels took place in a stepwise fashion, not apparent if a simple pulse chart is used. Since the interval between auricular fibrillatory waves ranges from 0.12 to 0.20 second, the possibility was considered that the level of 0.35 second produced after exercise corresponds to two fibrillation periods, and that the A-V nodal refractory period is between one and two fibrillation periods in duration. The other levels described may be regarded as an expression of 2:1, 3:1, 4:1 and 5:1 block.

The importance of the nodal refractory period, fibrillation period and ventricular (nodal) automatism, is discussed at length.

HELLERSTEIN

Israel, G. H., and Mazzei, E. S.: Auricular Paroxysmal Tachycardia with A-V Block. Schweiz. Med. Wchnschr. **80:** 954 (Sept.), 1950.

Twenty-five cases of auricular paroxysmal tachycardia with A-V block are analyzed in this study. This type of tachycardia seems to be more frequent in men (15 cases) than in women (10 cases), and is generally seen after the age of forty. The block is frequently a 2:1 A-V block, sometimes a 4:1 block, an irregular partial A-V block or Wenckebach's periods. It is generally seen in already damaged hearts (hypertensive heart disease and valvular disease) and its subjective symptoms are more pronounced than those of the usual type: palpitation, precordial pain and dizziness are frequent complaints. The duration of the attack varies from two hours to one year. Auricular fibrillation is frequently associated with auricular paroxysmal tachycardia with A-V block. The authors believe that quinidine is the most efficient drug in the therapy of this condition.

RITTER

Sturkie, Paul D.: Abnormal Electrocardiograms of Chickens Produced by Potassium Deficiency and Effects of Certain Drugs on the Abnormalities. Am. J. Physiol. **162:** 538 (Sept.), 1950.

Potassium deficiency in the diet of 2 to 4 day old chicks was followed in several days by electrocardiographic abnormalities in 19 of 42 birds examined. Morbidity was high early in the course of study, and

death occurred in all cases within 21 days. No gross abnormalities were demonstrable in the myocardium at necropsy. The electrocardiographic abnormalities included second degree atrioventricular block in 11 instances, complete atrioventricular block, premature beats, and sinus slowing. Diethylaminoethanol (DAE), presumably one of the breakdown products of procaine in the body, was administered intramuscularly to 10 chicks demonstrating electrocardiographic abnormalities. In every instance, repeated doses of 55 mg. (up to 165 mg. per animal) were followed by restoration of a normal sinus mechanism.

Ten 6 week old birds were also treated with potassium deficient diets. All cases showed electrocardiographic abnormalities within 18 days. The most frequent abnormalities consisted of ventricular extrasystoles.

Atropine sulfate (1 to 2 mg.) administered intramuscularly to 7 chicks and to 2 older birds normalized the electrocardiogram in four instances. Three died instantly following the injection. The 2 remaining animals failed to respond to atropine, but did respond to diethylaminoethanol. In 5 chicks treated with procaine hydrochloride (2 to 5 mg.), only 1 showed a partial response. In 2 animals not responding to procaine, diethylaminoethanol resulted in a normal sinus rhythm.

HECHT

Somerville, Walter: Effect of Cortisone on the Cardiogram. Brit. M. J. **2**: 860 (Oct.), 1950.

The author describes the effect of adrenal insufficiency on the heart and circulation, and mentions briefly its flattening effect on the T wave, prolongation of the Q-T interval, its effect in producing low voltage, prolongation of the P-R and QRS intervals, and its effect in depressing the S-T segment.

This study concerns 11 patients with chronic renal insufficiency who received cortisone therapy. Six of these presented electrocardiographic abnormalities prior to treatment, and in 4 of this group cortisone improved the cardiograms. In 1 the improvement persisted for five months after the treatment was discontinued. In 2 others, who had implanted pellets, the improvement was noted for two months after their use. In all, the improvement in the cardiogram partly regressed in two months. Heart size and blood pressure were unaffected by the therapy.

TANDOWSKY

McGregor, M.: The Genesis of the Electrocardiogram of Right Ventricular Hypertrophy. Brit. Heart J. **12**: 351 (Oct.), 1950.

The genesis of the electrocardiogram of right ventricular hypertrophy in 10 instances of Fallot's tetralogy was studied by placing an exploring electrode on the pericardium exposed by thoracotomy. The descending branch of the left coronary artery was considered to mark approximately the boundary zone between the two ventricles. An rS pattern was obtained from the right ventricular surface similar to that derived from the left precordium and a qR pattern was obtained from the left ventricular surface similar to complexes over the right chest. These findings support Kossman's suggestion of almost complete reversal of the electrical fields of the two ventricles in the thorax as a result of rotation of the heart.

SOLOFF

HYPERTENSION

Raab, W., and Lepeschkin, E.: Biochemical Versus Hemodynamic Factors in the Origin of Hypertensive Heart Disease. Acta med. Scandinav. **138**: 81 (June), 1950.

The term "hypertensive heart disease" implies a definite causal relationship between the high blood pressure level and coexistent cardiac abnormalities supposedly elicited by the hemodynamic load imposed upon the heart muscle. The significant electrocardiographic manifestations of hypertensive heart disease are found in a number of other conditions. All of these have myocardial anoxia or hypoxia in common, due either to an absolutely reduced oxygen supply to the heart muscle, or to an abnormally rapid oxygen consumption by the myocardium. The latter is a specific metabolic effect produced by the sympathomimetic neurohormones.

The authors have attempted to study the question of whether the electrocardiographic effects of hypertensive heart disease are due mainly to the mechanical hemodynamic load of the high blood pressure or to the effects of adrenosympathetic hypoxia upon the myocardium. In favor of the latter hypothesis, the authors point out that the electrocardiographic effects of vasopressor sympathomimetic amines correspond to the ventricular strain pattern and are independent of the behavior of the blood pressure. Vasodepressor sympathomimetic amines produce the same electrocardiographic effects. In addition, similar chemical alterations are found in the hearts of hypertensives and in heart muscle experimentally treated with sympathomimetic amines. Normalization of the electrocardiogram has been noted after sympathectomies which did not effect the hypertension. It is known that sympathectomy is followed by a marked diminution of the myocardial concentration of epinephrine-like catechols.

The authors conclude that the problem of hypertensive heart disease should be reconsidered from the standpoint of a biochemically elicited lesion, caused by cardiotoxic neurohormonal effects.

SCHWARTZ

Corcoran, A. C., Page, I. H., and Dustan, H. P.: Urinary Formaldehydogenic Corticoids: Normal

Values and Observations in Hypertension. J. Lab. & Clin. Med. **36:** 297 (Aug.), 1950.

The primary object of this study was the clarification of adrenal cortical function in hypertension. Urinary formaldehydogenic corticoids averaged 1.04 mg. per 24 hours in normal men and 0.56 mg. in normal women. The difference between the mean excretion rates in the two sexes was significant. The day and night urinary corticoid levels did not significantly differ. Repeated observations indicated an average variability of 24 per cent in normal subjects.

Hypercorticoiduria was a common finding in patients with essential and malignant hypertension. The increase of urinary corticoids in hypertension may be due to some inadequacy of corticoid conjugation and also to the stress of the disease. The variability of corticoiduria is increased in hypertension. The undue lability of corticoid excretion seems to be part of the biochemical pattern of the disease, and may be associated with the other evidences of vasomotor and sympathetic instability which are common in hypertension. This variability of urinary corticoids supports the concept that essential hypertension is a disease of multiple and complex (neurogenic, renal and endocrine) pathogenesis in which the adrenal gland is often involved.

MINTZ

Campbell, Allan: Treatment of Severe Hypertension with Hexamethonium Bromide. Brit. M. J. **2:** 804 (Oct.), 1950

After briefly reviewing the more recent hypotensive drugs, the authors chose hexamethonium bromide for this study because of its slower onset of action, combined with greater potency and longer duration of effect. It was demonstrated that this drug was capable of producing a marked and protracted reduction of systolic and diastolic blood pressure, and was given to 8 patients suffering from severe hypertension with papilledema. A dose of 100 mg. was given intramuscularly every four hours. This was followed by oral administration in gradually increasing dosage until the patient received a daily total of from 2 to 3 Gm. before meals. The authors claim that in the series studied headache was abolished, the papilledema markedly regressed, and vision was improved in every case. The entire 8 patients studied are now ambulatory. Withdrawal of the drug in 3 cases did not lead to immediate rise in pressure, and in 1 the pressure remained normal after eight weeks. Pentamethonium bromide and iodide were found less effectual.

Untoward symptoms occurred in all but were mild, consisting of blurring of vision, dry mouth, nausea, heartburn and constipation. Paralytic ileus was encountered in 2, necessitating withdrawal of hexamethonium for 24 hours and the use of high enemas. It is emphasized that medication must begin with small dosage to avoid circulatory collapse which occurred in 2 of this series. Although postural hypotension was evident when patients became ambulatory, it only lasted for a few days.

TANDOWSKY

Govaerts, J., and Hoffmann, G. R.: Cutaneous Thermometry in Arterial Hypertension. Acta cardiol. **5:** 419, 1950.

The authors studied, by means of cutaneous thermometry in four hypertensive patients, the type of reflex vasodilatation following immersion of the hands in warm water. In 2 cases a prevalent vasospastic factor was demonstrated by a sudden and marked increase of the cutaneous temperature. In the other 2 cases, the lack of instantaneous reaction seemed to indicate an organic vascular disease. The test appears to be of value in the selection of hypertensive patients for thoracolumbar sympathectomy.

PICK

PATHOLOGIC PHYSIOLOGY

Oster, K. A.: Influence of Castration on Blood Pressure. Cardiologia **16:** 329 (May), 1950.

The author found that castration in adult rats produced a significant temporary rise in blood pressure in the male, and a fall in blood pressure in the female. It is postulated that the changes may be due to a disturbance in the extracellular fluid balance. On the other hand, rat testes may contain a hormone which regulates the blood pressure in an antipressor fashion, and the ovaries of this species may contain a hormone which has a pressor effect on the systemic blood pressure. The return of the blood pressure level to normal in both castrated groups after a period of time suggests that some other gland may take over the regulation of blood pressure, correcting the disturbance originally caused by the removal of the sex gland.

SCHWARTZ

Eckstein, R. W., Stroud, M., III, Dowling, C. V., and Pritchard, W. H.: Factors Influencing Changes in Coronary flow Following Sympathetic Nerve Stimulation. Am. J. Physiol. **162:** 266 (Aug.), 1950.

The authors present experiments on dogs anesthetized with sodium pentobarbital in an attempt to evaluate the possible effect of physical factors upon coronary flow following accelerator nerve stimulation. They employed studies on fully dilated and cannulated coronary arteries in order to separate vascular from physical factors. A recording rotameter was used to measure blood flow.

Lengthening of diastole and shortening of systole produced increases in flow up to 30 per cent, but usually much less. Decreases of mid-diastolic intraventricular pressure of 4 to 5 mm. Hg accounted for no more than about 5 per cent increases in flow. Decreases in systolic and diastolic cardiac volume are probably without effect upon coronary flow. There is no positive evidence that the heart mas-

sages blood through itself, except for flow increases due to lengthening of diastole. Elevation of aortic pressure or increased cardiac output do not account for significant increases in coronary flow.

It is believed that these physical factors account for only a small portion of the increased coronary flow following accelerator nerve stimulation, and that the changes result chiefly from active coronary vasodilatation.

HECHT

Hwang, W., Akman, L. C., Miller, A. J., Silber, E. N., Stamler, J., and Katz, L. N.: Effects of Sustained Elevation of Renal Venous Pressure on Sodium Excretion in Unanesthetized Dog. Am. J. Physiol. **162:** 649 (Sept.), 1950.

Elevation of renal venous pressure, sustained for approximately one week by partial ligation of the vena cava in 16 trained unanesthetised dogs, was followed by only an initial reduction of renal blood flow, glomerular filtration rate, and sodium excretion. The values returned to normal sometime after the fourth postoperative day. The authors suggest that the reduced sodium excretion observed in congestive heart failure is not necessarily the result of an elevated renal venous pressure. The possibility remains, however, that sudden, repeated elevations of renal venous pressure may cause temporary but significant sodium retention which may contribute to the clinical syndrome of congestive heart failure.

HECHT

Wesson, Laurence G., Jr., Anslow, W. Parker, Jr., Raisz, Lawrence G., Bolomey, Alfred A., and Ladd, Michael: Effect of Sustained Expansion of Extracellular Fluid Volume upon Filtration Rate, Renal Plasma Flow and Electrolyte and Water Excretion in the Dog. Am. J. Physiol. **162:** 677 (Sept.), 1950.

A characteristic three-phase change in the glomerular filtration rate, renal plasma flow, electrolyte excretion and urine flow repeatedly followed the intravenous administration of a modified Locke solution in trained, unanesthetised dogs, resulting in sustained increase in the volume of extracellular fluid. The three-phase change was characterized by an initial marked increase in filtration rate and renal plasma flow. These functions returned to normal in phase two. The third phase was characterized by a secondary elevation of all three values to a level significantly above control levels. At a constant filtered load, and under conditions of maximum absorption activity due to the influence of daily administered Pitressin, sodium reabsorption in phases two and three was greater than is phase one. Associated with this finding was a 50 per cent reduction in sodium excretion. Despite the continuous administration of Pitressin, phase two was characterized by reduced water absorption, accompanied by a temporarily hypotonic urine.

Water reabsorption is influenced, apparently, by factors other than the antidiuretic hormone. Changes in blood pressure, reflecting arteriolar (renal) changes, along with changes in plasma proteins seem to be unrelated to the mechanism involved.

HECHT

Pfeiffer, J. B., Jr., and Wolff, H. G.: Studies in Renal Circulation during Periods of Life Stress and Accompanying Emotional Reactions in Subjects with and without Essential Hypertension; Observations on the Role of Neural Activity in Regulation of Renal Blood Flow. J. Clin. Investigation **29:** 1227 (Sept.), 1950.

The authors present a detailed report on renal function studies performed on 35 subjects. Twenty-three of this group were hypertensives, and none had evidence of renal disease. Six of the hypertensive group were studied before and after lumbodorsal sympathectomies and splanchnicectomies. During the performance of the tests, topics of emotional significance were discussed with the subjects.

Among the normotensives, an elevation of blood pressure was obtained in the majority during the experimental period. The average increase in mean pressure was about 10 per cent. The hypertensives responded with an increase in pressure which was not different from the normotensive group. With this elevation in pressure there was a constant fall in effective renal blood flow and rise in filtration fraction, indicating an increase in renal arteriolar resistance. The increase in renal vascular resistance was unequivocally greater in the hypertensive group. Following lumbodorsal sympathectomy and splanchnicectomy, induced elevations in systemic pressure were accompanied by a reversal; i.e., the filtration fraction fell and renal vascular constriction was less intense. The authors interpret this as failure of the efferent glomerular arteriole to participate in the response to emotional stress, although the afferent arteriole is responsive.

The authors conclude that the kidney under usual conditions has two somewhat independent vascular mechanisms available: (a) sympathetic control of the effect glomerular arteriole, and (b) humoral control of the afferent glomerular arteriole.

WAIFE

Foltz, E. L., Page, R. C., Sheldon, W. F., Wong, S. K., Tuddenham, W. J., and Weiss, A. J.: Factors in Variation and Regulation of Coronary Blood Flow in Intact Anesthetized Dogs. Am. J. Physiol. **162:** 521 (Sept.), 1950.

Coronary blood flow was determined by the nitrous oxide method in 30 anesthetized dogs, and the findings were correlated with a number of observations on cardiovascular function simultaneously obtained during right ventricular catheterization. Even under controlled conditions, a large variation in data was noted in 13 dogs re-examined at an interval

of three to four weeks. On single determination, high degrees of correlation were found between coronary blood flow and cardiac oxygen consumption (r = 0.879 in 30 observations, and 0.900 in 60 observations), suggesting a metabolic-regulating mechanism for coronary blood flow. A high degree of correlation was also observed between coronary blood flow and cardiac rate (r = 0.700), cardiac output (r = 0.742) and cardiac work (r = 0.775).

For dogs (14 to 33 Kg.), the following data may be regarded as normal values under Dial-urethane pentobarbital anesthesia: coronary blood flow, 85 cc. per 100 Gm. per minute; cardiac oxygen consumption, 9.3 cc. per 100 Gm. per minute; cardiac output, 2.85 cc. per minute; peripheral resistance, 3010 units; coronary resistance, 1.32 (ratio of coronary flow to arterial pressure); coronary atrioventricular oxygen difference, 11.4 volumes per cent; coronary oxygen utilization 69 per cent.

Dial anesthesia in morphinized dogs appeared to simulate a resting circulatory state; pentobarbital sodium anesthesia produced a situation comparable to moderate exercise.

HECHT

Patterson, J. L., Jr., Heyman, A., and Nichols, F. T., Jr.: Cerebral Blood Flow and Oxygen Consumption in Neurosyphilis. J. Clin. Investigation **29:** 1327 (Oct.), 1950.

Using the nitrous oxide method, a study of the cerebral circulation and metabolism was performed on 58 patients with various types of neurosyphilis and on 16 control subjects. In asymptomatic neurosyphilis, the mean cerebral blood flow, oxygen consumption and vascular resistance were within normal limits. The cerebral blood flow and the cerebral oxygen consumption, however, were significantly reduced in patients with dementia paralytica and meningovascular syphilis. Furthermore, there seems to be a definite correlation between the degree of mental deterioration and the reduction in cerebral oxygen consumption in patients with dementia paralytica. Treatment with penicillin and fever, accompanied by improvement in mental state, were also followed by a rise in the cerebral oxygen consumption. It was noted that 6 patients had mean cerebral oxygen consumption values below 2.0 cc. per 100 Gm. of brain per minute. Values of this order are usually associated with coma in patients with diabetic acidosis, insulin shock, or brain tumor; these individuals were conscious and capable of simple mental functions.

WAIFE

Effect of Auricular Fibrillation on Cardiac Output, Coronary Blood Flow and Mean Arterial Blood Pressure. Wegria, R., Frank, C. W., Misrahy, G. A., Sioussat, R. S., Sommer, L. S., and McCormack, G. H., Jr.: Am. J. Physiol. **163:** 135 (Oct.), 1950.

Mean arterial blood pressure was recorded simultaneously with two flowmeters (rotameters), which recorded mean output of the left ventricle and mean blood flow in the left anterior descending coronary artery during atrial fibrillation electrically induced in dogs. At the beginning of fibrillation, all three values fell, followed in a few seconds by some recovery toward control values. Since, at this time, coronary flow often excedes control values although arterial pressure and cardiac output remain low, it is concluded that coronary resistance is decreased. As the bout of fibrillation ends, all three measurements, with occasional exceptions in blood pressure, increase well above control values. The increase in mean arterial blood pressure can be shown to be due exclusively to an increase in cardiac output, since the calculated total peripheral resistance actually decreases at this time. Increase in coronary flow is attributed to increase in aortic blood pressure and/or increase in the work of the heart. In most cases, at the end of fibrillation coronary flow was the last to descend to normal levels following the post-fibrillation rise.

OPPENHEIMER

Grossman, J., Weston, R. E., Halperin, J. P., and Leiter, L.: The Nature of the Renal Circulatory Changes in Chronic Congestive Failure as Reflected by Renal Tubular Maximal Functions. J. Clin. Investigation **29:** 1320 (Oct.), 1950.

To determine whether or not the reduced renal hemodynamics in chronic congestive failure proportionately effects all nephrons, renal function studies were performed in 15 patients with rheumatic heart disease and well established chronic congestive failure. In this group the glomerular filtration rate and renal plasma flow were reduced. The maximal tubular capacity for excreting para-aminohippurate, a measure of functional tubular excretory mass, was, however, normal. Similarly the maximum tubular capacity for reabsorbing glucose, a measure of the number of functioning intact nephrons, was also within normal limits. These findings exclude the possibility of any significant intrarenal redistribution of blood.

The renal circulatory abnormality in chronic congestive failure apparently consists of generalized renal ischemia, with a decrease in filtration in the glomerulus of each nephron but without reduction in the tubular mass perfused. From the evidence cited here there appears to be a functional glomerulotubular imbalance which may greatly influence renal excretion of salt and water.

WAIFE

Fowler, N. O., Westcott, R. N., Hauenstein, V. D., Scott, R. C., and McGuire, J.: Observations on Autonomic Participation in Pulmonary Arteriolar

Resistance in Man. J. Clin. Investigation **29:** 1387 (Oct.), 1950.

A study was made of the effect of the autonomic blocking agent, tetraethylammonium chloride (TEAC) upon pulmonary arteriolar resistance. Cardiac catheterization was performed on 15 patients, of whom 5 were normal, 2 had pulmonary emphysema, 2, congestive heart failure, 1, pneumonia, 3, hypertensive vascular disease, 1, bronchiectasis, and 1, cor pulmonale. In 4 patients with normal pulmonary artery pressures, no decline was observed after TEAC. In 11 subjects, however, intravenous TEAC produced a sustained fall in mean pulmonary arterial pressure. In 4 of 6 subjects with pulmonary hypertension, TEAC caused a significant decrease in pulmonary arteriolar resistance. The effect of this agent on the cardiac output was variable. Four of 5 subjects studied by the ballistocardiograph developed abnormal patterns, suggesting a direct cardiac action of the drug in man. In each of 14 subjects, intravenous TEAC led to a decline in brachial arterial pressure. In 4 of these, however, the fall in pressure was due to a decline in cardiac output rather than to a decrease in total peripheral resistance.

The decline in pulmonary arteriolar resistance after TEAC in 4 of 6 cases with pulmonary hypertension indicates that in some such cases the increase in pulmonary arteriolar resistance is mediated in part through the autonomic nervous system.

WAIFE

Keys, A., Mickelsen, O., Miller, E. O., Hayes, E. R., and Todd, R. L.: The Concentration of Cholesterol in the Blood Serum of Normal Man and Its Relation to Age. J. Clin. Investigation **29:** 1347 (Oct.), 1950.

In order to provide the basis for more precise evaluation of total serum cholesterol determinations in persons of various ages, a survey of 5,000 measurements of total cholesterol in 2,056 persons is reported. The ages of the 1492 men ranged from 17 to 78 years, and the ages of the 564 women ranged from 17 to 30 years. Detailed physical examinations revealed these subjects to be physically normal. Most subjects were engaged in business, professional and scholastic activities, and represent a group of "responsible citizens" of an upper midwestern metropolitan area.

Over the age range 17 to 30, the cholesterol values in man and women were not significantly different. There was an average increase, per year of age, amounting to 2.2 mg. of total cholesterol per 100 ml. of serum. For the age range 17 to 78 years in men, there was a pronounced curvilinear relation between age and serum cholesterol concentration. The maximum was in the sixth decade. In the clinically normal persons from the population and environment studied, it appears that over the range of 45 to 70 years the cholesterol values of 1 per cent of the groups will exceed 320 mg. Between the ages of 45 and 60, the values in 5 per cent of normal men will exceed 300 mg. Thus at age 60, 90 per cent of the population would have a cholesterol determination from 197 to 309 mg. per 100 ml. At that age, 98 per cent of the population would have a serum cholesterol concentration of from 173 to 333 mg. per 100 ml.

WAIFE

Asali, N. S., and Prystowsky, H.: Studies on Autonomic Blockade. I. Comparison Between the Effect of Tetraethylamonium Chloride (TEAC) and High Selective Spinal Anesthesia on Blood Pressure of Normal and Toxemic Pregnancy. J. Clin. Investigation **29:** 1354 (Oct.), 1950.

High spinal anesthesia induced by 0.2 per cent procaine selectively blocks vasoconstrictor fibers. When this method was compared with the effect of tetraethylammonium chloride (TEAC) which blocks the autonomic ganglia, it was found that, in normal pregnant women and patients with toxemia of pregnancy in the prepartum and postpartum periods, the effect on the blood pressure was practically parallel. There was a negligible fall in blood pressure of normotensive, nonpregnant and toxemic subjects, but marked hypotension with bradycardia in normal pregnant women in the prepartum, followed by a return of blood pressure responses to normal in the postpartum period. The authors feel that the lack of blood pressure response of most toxemic patients to high selective spinal anesthesia adds more evidence to the humoral theory of toxemic hypertension.

WAIFE

PATHOLOGY

Spang, K., and Gabele, A.: Post War Endocarditis a Special Form of Endocarditis Lenta. Arch. f. Kreislaufforsch. **16:** 52 (May), 1950.

During the first years following World War II the authors observed an increased incidence of endocarditis; certain features suggested that the involvement was a special form of subacute bacterial endocarditis. It occurred mainly in males, ran a protracted and not always fatal course, and showed a tendency to produce a leukopenia and only slight elevations of the temperature. The spleen was usually enlarged, but the blood cultures remained sterile for the most part. Cardiovascular signs and heart failure were prevalent from the beginning, and renal involvement and insufficiency developed in the later course of the disease. Thromboembolic phenomena and an elevation of the sedimentation rate were as frequent as in typical cases of bacterial endocarditis. Treatment with sulfonamides proved successful in a few cases. In the opinion of the authors the high incidence of this type of endocarditis and its particular clinical course can be ascribed to a decreased re-

sistance of the general population and an altered reactivity to infections, as a result of poor living conditions during and after the war.

PICK

Martensson, J.: Cardiovascular and Renal Findings in Long-Standing Diabetes Mellitus. A Study of 221 Patients Surviving at Least 15 Years. Acta med. Scandinav. **138:** 94 (June), 1950.

The author investigated the incidence and nature of the complications involving the heart, blood vessels, and kidneys in a series of 221 cases of diabetes of 15 to 34 years duration. The patients ranged in age from 16 to 84 years. Hypertension was found in 48 per cent of the 111 men, and in 65 per cent of the 110 women studied. Definite signs of coronary arteriosclerosis were seen in 82 patients, 11 of whom also had myocardial infarction. In 42 cases gangrene, chronic ulceration, or severe arterial insufficiency of the lower extremities was noted. Amputation was necessary in 14 cases. Nephropathy was found in 71 cases, and of 30 cases examined post mortem, 7 presented evidence of intercapillary glomerulosclerosis.

SCHWARTZ

Fenichel, N. M.: Arteriosclerotic Aortic Insufficiency. Am. Heart J. **40:** 117 (July), 1950.

The author presents a series of 17 patients with aortic insufficiency, presumably of arteriosclerotic origin. All were in the older age group (59 to 75 years), and had hypertension and peripheral arteriosclerosis. There was no evidence of syphilitic or rheumatic infection. Physical findings included a widened pulse pressure, aortic systolic murmurs (average grade III), and an aortic diastolic murmur usually heard best at Erb's area in the third intercostal space to the left of the sternum or directly over the aortic area. The latter was of short duration, distinctly diminuendo, and not to be confused with a reduplicated second sound. Angina pectoris, myocardial infarction, and congestive heart failure were common. In most instances, the advent of the aortic valvular insufficiency had little adverse influence on the prognosis. Autopsy findings on one case showed dilatation and sclerosis of the aorta, calcific aortic valvular stenosis and insufficiency of arteriosclerotic origin. The possibility is mentioned that some of these patients might have had rheumatic infection without a clinical history.

HELLERSTEIN

Baldwin, D., Taylor, C. B., and Hass, G. M.: A Comparison of Arteriosclerotic Lesions Produced in Young and in Old Rabbits by Freezing the Aorta. Arch. Path. **50:** 122 (July), 1950.

The authors, employing their special technic of producing sharply localized segmental injury in the aorta of rabbits by carbon dioxide freezing, studied such effects in senescent rabbits. The reaction, similar to that noted in younger rabbits, could be divided into degenerative and regenerative phases. In old rabbits the degenerative process differed in the tendency toward the formation of bone and cartilage in the adventitia, previously not noted in young animals, and independent of medial calcification which was present in young and old rabbits alike. Another striking difference in the regenerative phase in old rabbits was the slow and relatively slight hyperplasia of the intima from which as a matrix the entire aortic wall had completely regenerated in young rabbits. Smooth muscle elements in the intima regenerated well, elastic regeneration was slight, and formation of an internal elastic lamella was limited. To that extent regeneration in old rabbit aortas was impaired, and localized aneurysmal dilatations were only partly filled in by the reparative process.

GOULEY

Miller, G., Becker, I. M., and Taylor, H. K.: Auricular Calcification. Am. Heart J. **40:** 293 (Aug.), 1950.

The authors present 8 cases of left auricular calcification, 5 with postmortem studies. All had chronic rheumatic heart disease with auricular fibrillation and longstanding congestive heart failure. Roentgenographic examination showed circular calcific deposition within the central portion of the cardiac silhouette in the anteroposterior projection and in the posterior portion in the lateral projection, i.e., the area of the left auricle. Postmortem examination of 5 cases revealed stenosis and insufficiency of the mitral, and aortic or tricuspid valves; mural thrombosis of the left auricle was found in 4 cases. The occurrence of left auricular calcification is believed to be secondary to rheumatic auriculitis and mural thrombosis.

HELLERSTEIN

Clifford, W. J., MacGillivray, W. F., and Goodale, R. H.: Aneurysm of the Pulmonary Artery. Am. J. Roentgenol. **64:** 414 (Sept.), 1950.

The authors report a case of aneurysm of the trunk and left branch of the pulmonary artery in a young woman with recurrent pulmonary infections, pulmonary hypertension, apparent recurrent pulmonary embolizations, progressive right ventricular and right atrial enlargement, and increased size of the pulmonary artery segment, which even five days before death was not unusually prominent, and certainly not of sufficient size or configuration to suggest aneurysm.

Postmortem examination indicated a sacular dilatation of the pulmonary artery (measuring 5 cm. in diameter) and the proximal portion of its left branch, right ventricular and right atrial hypertrophy and dilatation, pulmonary fibrosis, and evidence of severe pulmonary hypertension.

SCHWEDEL

Baron, E. and Ritter, D. W.: Endocardial Tuberculosis. Ann. Int. Med. **33:** 1023 (Oct.), 1950.

A 53 year old Negro, with a past history of hypertension and repeated bouts of heart failure, was admitted to the hospital with symptoms suggestive of a cerebrovascular accident. The blood pressure was intermittently elevated; systolic and diastolic cardiac murmurs were audible; an inconstant extrasystolic arrythmia, ventricular in type, was present; there was persistent fever without any elevation of the white blood cell count. Tuberculosis was not suspected during life. The significant necropsy findings consisted of: (a) tuberculoma in the left auricular appendage, which was fused to the auricular endocardium without penetrating the myocardium; (b) a tuberculoma of the brain; (c) a tuberculoma of the spleen; (d) miliary tubercles in the lungs, liver, spleen, adrenal and kidney; (e) tuberculous involvement of the small arterioles of the lungs; (f) marked hypertrophy of the ventricular myocardium and (g) sclerotic and calcified arteries.

WENDKOS

PHARMACOLOGY

Schaffer, A. I., Steinman, R., and Scherf, D.: Intravenous Procaine: Its Effect on the Human Electrocardiogram and on Cardiac Arrhythmias. Cardiologia **16:** 341 (May), 1950.

The authors investigated the effect of intravenous procaine on the electrocardiogram and on arrhythmias in unanesthetized hospital patients. One group of 11 patients received an intravenous drip of 300 to 500 mg. of procaine hydrochloride within 8 to 30 minutes. Another group of 21 patients received 85 to 100 mg. intravenously as a 1.0 per cent solution within 12 seconds or less.

Procaine, in the dose and speed given, rarely caused threatening changes in the electrocardiogram. It did not significantly influence auricular flutter or paroxysmal tachycardia. The decrease of auricular rate in flutter may result, however, in the conduction of more stimuli to the ventricles and a consequent increase of ventricular rate. On the other hand, procaine may temporarily depress A-V conduction, with a resultant decrease of the ventricular rate in flutter. The appearance of auricular and ventricular extrasystoles with procaine indicates the necessity for caution in the use of large doses.

The authors conclude that procaine in the doses used depressed ectopic stimulus formation only to a very limited extent.

SCHWARTZ

Harken, D., and Norman, L.: The Control of Cardiac Arrhythmia during Surgery. Anesthesiology **11:** 321 (May), 1950.

To apply rational therapy, abnormal rhythms must be properly identified. The cause of an arrhythmia must also be identified. Causes may include reflexes, chemical changes in the blood, or direct cardiac manipulation. The heart may be protected by a number of prophylactic measures, which include the regulation of fluid and electrolyte balance, and the proper use of digitalis or quinidine.

During surgical procedures on the heart itself, the authors have come to lean heavily on procaine to prevent arrhythmias. In anticipation of the occurrence of arrhythmias, there should be a definite plan of action. Emergencies fall into the categories of prefibrillatory states, ventricular fibrillation, and cardiac standstill. Treatment is discussed, and the role of procaine in the control of arrhythmias considered.

Resuscitation of the heart from asystole involves: (a) adequate oxygenation; (b) removal of the stimulus; (c) cardiac massage; and (d) reinforcement of the heart beat. If ventricular fibrillation is present, another plan must be carried out, involving direct procaine injection, massage, and electric shock.

KING

Capps, R. T., Kozelka, F. L., and Orth, O. S.: Chronic Toxicity of Thiomerin Compared to Other Mercurial Diuretics. Proc. Soc. Exp. Biol. & Med. **74:** 511 (July), 1950.

According to this report on the comparative toxicity of Thiomerin, Mercuhydrin and Mercurophylline, the compound containing the thiol group is definitely more toxic in rats. Sodium Thioglycolate (monothiol compound) potentiated the chronic toxicity of Mercurophylline when combined with it and given by either the subcutaneous or intravenous route. The toxicity of this combination of mercurial and thiol was the same as that of Thiomerin. The addition of the thiol compound, even though it eliminates the danger of acute death following intravenous injections, so increases the chronic toxicity of Mercurophylline by either subcutaneous or intravenous routes that its addition would seem to be a hazard. Studies of the distribution of mercury in the rat and its excreta following subcutaneous administration of Thiomerin and Mercurophylline failed to indicate the mechanism of potentiation of toxicity.

MINTZ

Reiner, M.: Effect of Cortisone and Adrenocorticotropin Therapy on Serum Proteins in Disseminated Lupus Erythematosus. Proc. Soc. Exper. Biol. & Med. **74:** 529 (July), 1950.

The electrophoretic distribution of the serum proteins in 20 patients with disseminated lupus erythematosus showed a lowered albumin content with a considerable increase in the $alpha_2$ as well as the gamma globulin concentration while the $alpha_1$ and beta globulin remained within the normal range. The sera of 5 patients were studied before therapy with cortisone and ACTH. After a clinical remission was produced by cortisone and ACTH, the albumin and gamma globulin components progressed toward

normal levels, whereas the alpha$_2$ globulin fraction remained unchanged.

MINTZ

Murphy, Q., O'Brien, G., and Meek, W.: The Effects of Aliphatic Sympathomimetic Amines on Cardiac Automatic Tissue in Dogs under Cyclopropane. Anesthesiology **11:** 437 (July), 1950.

Cyclopropane is known to sensitize ventricular automatic tissue to certain of the cyclic sympathomimetic amines. In this series, seventeen straight-chain amines were studied to see if similar effects occurred with these aliphatic amines. Aranthol, Tuamine, and 2-methylamino-1-cyclopentylpropane were selected for detailed study.

Cyclopropane appeared to sensitize the ventricle to eleven of these amines, including Aranthol and Tuamine, just as it does to epinephrine; 2-methylamino-1-cyclopentylpropane, in addition to three other aliphatic amines, showed no evidence of producing ventricular stimulation. Except for 3-aminoheptane which was found to be too toxic for use, and 2-aminooctane which was depressor under cyclopropane, all the aliphatic amines studied produced a marked sinoauricular tachycardia during anesthesia.

KING

Green, D. M., Johnson, A. D., Bridges, W. E., Lehman, J. H., and Gray, F.: Mechanisms of Desoxycorticosterone Action: Effects of Water Soluble Glycoside on Human Circulatory and Renal Functions. Endocrinology **47:** 102 (Aug.), 1950.

The authors wished to clarify the contradictory effects of desoxycorticosterone acetate which have been reported in relation to water excretion, sodium excretion and glomerular filtration. The glycoside of desoxycorticosterone (DCG) was used because its water solubility allowed large intravenous doses to be given and immediate effects produced, thus enabling direct effects to be distinguished from compensatory reactions.

Thirteen fasting human subjects were used, and after baseline circulatory and renal functional values were determined, DCG was given intravenously at a constant rate of 20 mg. per square meter per hour, and the various measurements repeated during three 20 minute periods. There was an early, transitory rise in filtration rate, associated with a small increase in peripheral resistance and a fall in cardiac output. A second effect was a reduction in tubular reabsorption of water, which became most evident when the elevated water output persisted after the filtration rate returned toward control levels. The third effect was on sodium excretion, the net change being the resultant of the rise in sodium excretion associated with the increase in water excretion and filtration rate, the fall in urinary sodium concentration, and the later fall in total sodium excretion in the presence of increased water output. The latter was interpreted as an indication of relative increase in tubular reabsorption of sodium. There was no significant effect on systemic blood pressure.

CORTELL

Littmann, D. and Schaaf, R. S.: Therapeutic Experiences with Subacute Bacterial Endocarditis with Special Reference to the Failures. New England J. Med. **243:** 248 (Aug.), 1950.

This study comprises a statistical review of the experiences with subacute bacterial endocarditis during the period of 1947 to 1949 as compared with the period of 1944 to 1946. The authors found that the incidence of this disease had decreased by 50 per cent during 1947 to 1949. Of 75 patients with subacute bacterial endocarditis who received adequate treatment, 52 recovered. Seventeen of the 23 failures showed irreversible cardiac, renal or cerebral changes. When congestive failure and uremia occurred during therapy, the prognosis was found to be poor. The nutritional status of the patients was related to the severity of the disease; poorly nourished patients accounted for a high percentage of the failures. The occurrence of bacterial resistance was considered to have developed in 4 patients who died.

The severity of heart disease was considered to be the most important single factor influencing recovery. A high incidence of congenital bicuspid aortic valves was present in the group who died.

NADLER

McCoy, G. E., and Baidyeman, M. C.: Use of Drugs in the Diagnosis and Treatment of Pheochromocytoma. Pediatrics **6:** 286 (Aug.), 1950.

The authors describe the case of a 13 year old white boy with hypertension, who had a pheochromocytoma successfully removed from the left adrenal. Ambulation was begun on the second postoperative day, and the blood pressure began to increase. It was felt, therefore, that this child had another pheochromocytoma. Benzodioxane and Dibenamine, which caused a fall in blood pressure preoperatively, were ineffective, and histamine did not cause a rise in blood pressure.

After surgical removal of a solitary pheochromocytoma, hypertension may persist in a milder state. This is explained on the basis of secondary, but not permanent, changes in the vascular tree, and may or may not be reversible, depending on the severity and duration of the hypertension. It was emphasized that Dibenamine will produce a decrease in blood pressure in patients in the upright position with or without hypertension. The diagnosis of pheochromocytoma can be considered, therefore, only in patients who have a decrease in blood pressure with Dibenamine when they are in the supine position.

MARGOLIES

Engel, A.: Diagnostic Value of Increased Urinary Output of Noradrenaline and Adrenaline in Pheochromocytoma. Lancet **2:** 387 (Sept.), 1950.

These investigators believe that, inasmuch as the demonstration of an increased production of biologically active catechol derivatives is essential for the diagnosis of pheochromocytoma, their presence in increased quantity in the urine when adrenaline and other catechols are administered to man in conjugated forms suggests a new diagnostic approach to this disease. After acid hydrolysis of the urine and adsorption on alumina, the catechols in normal urines were demonstrated by biologic estimation to consist largely of noradrenaline.

Two cases were observed, in both of which a great increase in noradrenaline adrenaline output was noted, and pheochromocytoma was demonstrated surgically and histologically. Following surgery, the urinary output returned to normal in both cases.

TANDOWSKY

Prochnik, G., Maison, G. L., and Stutzman, J. W.: Carotid-Occlusion-Pressor Reflex: Influence of Existing Mean Arterial Pressure, of Anesthetics and of Ganglionic- and Adrenergic-Blocking Drugs. Am. J. Physiol. **162:** 553 (Sept.), 1950.

The pressor response in anesthetized dogs following bilateral occlusion of the carotid arteries proved to be directly related to pre-existing mean arterial pressures. This relationship was not different under pentobarbital or urethane administered intravenously or under ether given by inhalation. The adrenergic blocking agents DHO 180 (1 to 3 mg. per Kg.) and Dibenamine (2 to 4 mg. per Kg.) and the ganglionic blocking agent tetra ethyl ammonium (5 to 15 mg. per Kg.) effectively suppressed the pressor response, and scattered the relationship of the pressor response to the mean arterial resting pressure.

HECHT

Sutton, G. C., Kappert, A., Reale, A., Skoglund, C., and Nylin, G.: Studies on L-Nor-Epinephrine: Relation of Dosage to Pressor and Bradycardia Effect. J. Lab. & Clin. Med. **36:** 460 (Sept.), 1950.

In this study, the intensity of action of norepinephrine in normal man was examined. Twenty-five studies were made on 21 normal men and 5 normal women. The blood pressures and pulse were recorded during and after the norepinephrine injection. Four different total dosages were employed: 0.1 mg., 0.07 mg., 0.05 mg., and 0.035 mg. This is equivalent to the administration of 0.02, 0.014, 0.01 and 0.007 mg. per minute respectively.

Irrespective of the dosage, the only response obtained consisted of an elevation of both systolic and diastolic blood pressures and a slowing of the heart. Both the systolic and diastolic pressures rose quickly to a steady level and remained elevated for the duration of the injection. This rise was accompanied by a feeling of deep pressure in the epigastrium and heavy breathing. The change in the pulse pressure during the hypertension was negligible. The heart rate decreased gradually, and the full effect was reached in a mean time of three minutes. Following the cessation of the injection, the after effect consisted of a direct return to prior resting levels within an average time of 1.6 to 5.0 minutes respectively for the smallest and largest doses.

These observations emphasize the difference between the action of norepinephrine and epinephrine. The results indicated that a dosage of 0.01 to 0.014 mg. per minute should be used in order to avoid untoward reactions.

MINTZ

Friedman, M., Byers, S. O., and Michaelis, F.: Observations Concerning Production and Excretion of Cholesterol in Mammals. II. Excretion of Bile in the Rat. Am. J. Physiol. **162:** 575 (Sept.), 1950.

A method for continuous cannulation of the bile duct of the unanesthetized rat is described. The average biliary pressure in 8 rats was 23 cm. of bile. The average bile flow (9 rats) was 15.5 cc. per rat or 5.03 cc. per 100 mg. in 25 hours. The average specific gravity was 1.011, and the pH was 8.3. Nearly all cholesterol was present in free form, averaging 12.7 mg. per cent (8.1 to 18.0 mg. per cent). Total biliary excretion of free cholesterol in 24 hours averaged 1.83 mg. (1.21 to 2.80 mg. per 24 hours).

HECHT

Raab, W., Humphreys, R. J., and Lepeschkin, E.: Potentiation of Pressor Effects of Nor-Epinephrine and Epinephrine in Man by Desoxycorticosterone Acetate. J. Clin. Investigation **29:** 1397 (Oct.), 1950.

The average pressor effects of both l-norepinephrine and epinephrine (0.1 to 0.3 μg. per Kg. per minute) in 12 nonhypertensive and 3 borderline hypertensive males were significantly intensified after the administration of desoxycorticosterone acetone acetate (10 mg. daily over an average of 17 days). Addition of extra salt to the diet did not appreciably influence this reaction.

The authors discuss the possibility that a potentiation of sympathomimetic pressor effects under the influence of exaggerated adrenocortical activity may be a pathogenic factor in essential hypertension.

WAIFE

Soffer, L. J., Levitt, M. F., and Baehr, G.: Use of Cortisone and Adrenocorticotropic Hormone in Acute Disseminated Lupus Erythematosus. Arch. Int. Med. **86:** 558 (Oct.), 1950.

Fourteen patients were included in this group. Six were treated with cortisone and then ACTH. One was treated with ACTH and then cortisone. Five received ACTH only and 2 had cortisone alone, The results were the same. With cortisone, however, 2 to 4 days were required for evident effects whereas

equal results were achieved with ACTH in 12 to 18 hours. Relapse after cessation of therapy was rapid with ACTH and slower with cortisone. Dosage was 150 to 200 mg. daily of cortisone or 100 to 150 mg. daily of ACTH divided into four doses. After the disease was under control for several weeks, the dose was reduced until minimum requirements were established. Therapy could not be discontinued without the occurrence a relapse.

Weight gain and edema, hypertension, congestive heart failure and alkalosis were noted in various patients during therapy. Nine of the patients developed euphoria, but the rest suffered depressions. Convulsions were seen in 4 patients. Prolongation of the Q-T interval was common. Moon face, striae, hirsutism, acne and pigmentation were also noted. Diabetes developed in only one case. The authors feel that no cures resulted from this form of therapy, since autopsies on 2 treated cases showed no differences from those on untreated cases. In spite of the presence of remissions, lupus cells, anemia, thrombocytopenia and abnormal urinary findings persisted. The sedimentation rate returned to normal levels only infrequently. In this series, one patient died of inadequate treatment, one because of intercurrent infection.

From this study it appears that long range or even permanent treatment may be necessary to control the disease.

BERNSTEIN

Merrill, J. P., Levine, H. D., Somerville, W., and Smith, S., III,: Clinical Recognition and Treatment of Acute Potassium Intoxication. Ann. Int. Med. **33**: 797 (Oct.), 1950.

The syndrome of potassium intoxication is encountered in clinical practice when there is impaired excretion of potassium in the presence of increased mobilization or intake of this electrolyte. In the 9 illustrative cases included in this report, the hyperkalemia was the result of oliguria, the causes of the oliguria being focal glomerulonephritis (1 case), chronic pyelonephritis (1 case), acute alcoholism (1 case), postoperative shock (2 cases), incompatible blood transfusion (2 cases), toxemia of pregnancy (2 cases). All 9 patients received infusions of hypertonic saline and glucose along with insulin. Hemodialysis with an artificial kidney was also employed in 6 of the cases. Of the 9 cases, 4 died. Hemodialysis was employed in 2 who died and in 4 who recovered. It is concluded that hemodialysis, by removing excess circulating potassium and toxic metabolites, augments the beneficial effects of glucose and saline.

The fact that potassium intoxication depends on both an elevation of serum potassium and a concomitant lowering of the serum sodium explains the finding that certain characteristic changes in the electrocardiogram were of more value than an estimation of blood in detecting the presence of potassium intoxication in these cases. Furthermore, the disappearance of such changes in serial electrocardiograms provided the best measure of effectiveness of the therapy being employed in any particular case.

Since such characteristic changes in the electrocardiogram constituted the earliest evidence of the onset of the clinical syndrome of potassium intoxication in the oliguric cases included in this report, it is recommended that frequent electrocardiograms be made in all patients with oliguria or anuria, so that the condition can be recognized and appropriately treated as soon as possible.

WENDKOS

PHYSICAL SIGNS

Holldack, K.: Increased and Decreased Intensity of the First Heart Sound. Schweiz. med. Wchnschr. **80**: 303 (March), 1950.

The author believes in the valvular origin of the first heart sound. In this article, he describes mitral stenosis with increased and with decreased intensity of the first heart sound. One of the causes of decreased intensity of the first heart sound in mitral stenosis is extensive calcification of the mitral valves. When calcification is limited to the free margins of the mitral valves, there is no decrease in intensity.

RITTER

PHYSIOLOGY

Steele, J. M., Berger, E. Y., Dunning, M. F., and Brodie, B. B.: Total Body Water in Man. Am. J. Physiol. **162**: 313 (Aug.), 1950.

Total body water, as measured by antipyrine space, was determined in 51 healthy men and 31 healthy women ranging from 20 to 80 years of age. The average per cent body water (as per cent of body weight) was 52.7 per cent for men, and 44.6 per cent for women. There was no correlation with age. Three successive determinations were made on each of 4 individuals, 48 to 72 hours apart; the results agreed within 8 per cent. Nine patients with edema due to various diseases had 58 to 71 per cent total body water. No determinations were made during and after diuresis.

The variations observed in normal individuals may be due to variation in the amount of body fat; the more fat, the less water. This variation in body fat was thought to account for the difference noted between men and women. The variation of total body water in normal subjects from person to person was greater than that between normal subjects and edematous patients.

HECHT

Berger, E. Y., Dunning, M. F., Steele, J. M., Jackenthal, R., and Brodie, B. B.: Estimation of Intracellular Water in Man. Am. J. Physiol. **162**: 318 (Aug.), 1950.

An estimation of intracellular water was made on

51 normal men and 31 normal women by measuring the extracellular space and comparing it with the total body water. The intracellular water compartment calculated from total body water minus sodium bromide space appears too small to account for the intracellular water of the various organs. It was concluded that the bromide space is considerably larger than the actual extracellular space.

Studies on inulin space indicate that approximately 20 hours are required for the inulin to equilibrate; since the starch is excreted rapidly in the urine, this method requires a prolonged, constant infusion of inulin. In nephrectomized dogs, in human subjects with severe renal insufficiency, and in normal humans, the inulin space was considerably smaller than the bromide space.

The extracellular space calculated on the basis of inulin was found to average 15 per cent of body weight in 4 human subjects. The intracellular water calculated, as the difference between total water and inulin space in these 4 subjects, was approximately 40 per cent of body weight or three-fourths of the total body water.

HECHT

Opdyke, D. F., Van Noate, H. F., and Brecher, G. A.: Further Evidence that Inspiration Increases Right Atrial Inflow. Am. J. Physiol. **162:** 259 (Aug.), 1950.

An analysis of phasic changes of effective right atrial pressure in anesthetized dogs provides indirect evidence that right atrial inflow increases during inspiration. The factor of atrial outflow was eliminated by measuring the effective atrial pressure gradient during ventricular systole. This pressure increased with the first heart beat after inspiration began, and thereafter decreased. The atrial volume-elasticity factor was considered to be negligible. The increased pressure was thought to be due to increased right atrial inflow and not to increased pulmonary resistance, because it occurred before the ventricle had ejected blood into the pulmonary circuit. In addition, a Valsalva experiment was accompanied by an increase in the right atrial pressure gradient without significantly changing chest size. The increase was thought to be independent of changes in hydrostatic level of the heart because even greater right atrial pressure gradient changes occurred when the heart shifted only slightly in position.

HECHT

RHEUMATIC FEVER

Tseng, J. Z. S., Elghammer, H. W., and Ivy, A. C.: Urinary Excretion of Glucuronic and Salicylic Acids in Normal and in Rheumatic Children. Am. J. Dis. Child. **79:** 826 (May), 1950.

Glucuronic acid determinations were performed on 24 hour urine specimins from 24 normal children, 3 children with tonsillitis, pharyngitis and sinusitis, and 47 children with rheumatic fever in various degrees of activity. The average output was 231 mg. for the normal children, 260 mg. (the increase is not considered statistically significant) for those with "inactive" disease, and 321 mg., for those with "active" rheumatic fever. The output was also increased in 1 child with tonsillitis, 1 with sinusitis, and 1 with pharyngitis. The increased urinary excretion of glucuronic acid in patients with active rheumatic fever was not considered specific because the patients with tonsillitis, pharyngitis and sinusitis also showed a definite rise. Acetylsalicylic acid administration produced a definite increase in the glucuronic acid excretion. When two parts of sodium bicarbonate were administered with one part of acetylsalicylic acid, there was a decrease in the plasma level of salicylic acid, a similar increase in the total urinary excretion of salicylic acid, and a decrease in the excretion of glucuronic acid. The administration of sodium bicarbonate with acetylsalicylic acid seemed to decrease the demand for glucuronic acid synthesis. Glucuronic acid excretion was not significantly affected by the administration of ascorbic acid to patients with rheumatic fever. No difference was discerned in the ability of children with active and inactive rheumatic fever to excrete glucuronic acid when acetylsalicylic acid was administered.

The authors conclude that alteration in glucuronic acid metabolism in patients with rheumatic fever should not be considered specific for the differential diagnosis of this disease.

MARGOLIES

Robertson, H. F., and Schlamowitz, S. T.: Rheumatic Nephritis. Ann. Int. Med. **33:** 708 (Sept.), 1950.

During a 170 day period in a military hospital, a 25 year old Negro man manifested fever with a disproportionate tachycardia, leukocytosis, increased sedimentation rate, carditis as evidenced by transient gallop rhythm, a systolic murmur at the apex varying in quality and intensity, a diastolic murmur over the aortic area, a slight prolongation of the P-R interval (0.25 second) in one electrocardiogram, pneumonitis of one lung, a poor response to penicillin and a favorable response to intravenous sodium salicylate, and all the laboratory evidences of an acute glomerulonephritis with an associated nephrotic element. By the end of his hospital stay, all urinary abnormalities and disturbed blood chemistry values had disappeared and his blood pressure had returned to normal levels. The associated carditis strongly suggests that the nephritis was causally related to an acute rheumatic episode.

WENDKOS

Quinn, R. W., and Liao, S. J.: A Comparative Study of Antihyaluronidase, Antistreptolysin "O," Antistreptokinase, and Streptococcal Agglutination

Titers in Patients with Rheumatic Fever, Acute Hemolytic Streptococcal Infection, Rheumatoid Arthritis and Non-Rheumatoid Forms of Arthritis. J. Clin. Investigation **29**: 1156 (Sept.), 1950.

The authors present the results of a comparative study of the four streptococcal antibody titers in 314 patients, 86 of whom had active rheumatic fever, and 56 of whom had rheumatoid arthritis. In active rheumatic fever, all four antibodies were found in high titer; in rheumatoid arthritis only the agglutination titer was high; in nonrheumatoid arthritis none of the antibody titers was consistently elevated.

The antihyaluronidase test measures a specific antibody, and a rise in this titer was demonstrated following the hemolytic streptococcal infection of the respiratory tract. Patients with active rheumatic fever had a significantly higher mean antihyaluronidase titer than any other group of patients studied. The three antienzyme titers remained high for considerably longer periods of time in patients who acquired rheumatic fever following hemolytic streptococcal infection than in patients who recovered from these infections without rheumatic complications.

WAIFE

Sprague, H. B., and Carmichael, D. B.: Rheumatic Valvular Disease of the Aged. Geriatrics **5**: 239 (Sept.–Oct.), 1950.

In 115 of 1,025 consecutive autopsies in patients over 50 years of age, the authors found evidence indicative of recent or old rheumatic heart disease. Only 112 charts were available for statistical analysis. Twenty-five per cent had a history of rheumatic fever in youth. The authors suggest an atypical rheumatic infection, or a variant of the classical course of rheumatic heart disease, because of the low incidence of childhood rheumatic fever, the infrequency of recurrences, the prolonged life, and the infrequency of death attributable to rheumatic cardiac involvement. Clinical evidence of cardiac failure occurred in 70 (61.6 per cent), but prolonged periods were rarely seen. There were 25 cases (21.7 per cent) with anatomic stenosis of the mitral valve. Aortic stenosis was found in 29 or 25.2 per cent of the cases. Four of these patients, aged 90, 80, 76, and 62 years, had a concomitant mitral stenosis. Auricular fibrillation occurred in 25 cases, in all of which there was evidence of congestive failure prior to death. Acute bacterial endocarditis was found in 11 of the 1,025 autopsies. Subacute bacterial endocarditis was found in 7, and in 6 it was grafted on rheumatic valves.

The authors conclude that an active life for an individual with rheumatic valvular damage, in the absence of cardiac insufficiency or active rheumatism, has no deleterious effect upon the ultimate prognosis.

MARGOLIES

ROENTGENOLOGY

Buchs, S., and Frommherz, G.: The Technical Aspects of Angiocardiography: Its Indications and Contraindications. Schweiz. med. Wchnschr. **80**: 347 (April), 1950.

The authors describe an apparatus which is basically a kind of huge rollfilm camera. It can take as many as 17 exposures in 1.5 seconds. Its construction is relatively simple and cheap and its operating costs are less than those of the angiocardiograph with the cassettes. It is nearly noiseless and all film sizes can be used. The film is moved mechanically, but all the other movements of this apparatus are controlled electromagnetically.

RITTER

Wise, R. E., Hughes, C. R., and Haman, J. R.: Cerebral Arteriography. Am. J. Roentgenol. **64**: 239 (Aug.), 1950.

The authors discuss the technical details of cerebral arteriography and review the findings in 150 arteriograms. In 38, tumors were revealed, in 25, aneurysms, in 8, vascular anomalies, in 8, arteriovenous fistulas, and in 1, thrombosis of the middle cerebral artery. The remaining arteriograms were normal or inconclusive because of technical difficulties.

Arteriography is a relatively simple and safe procedure. It provides adequate data for localization of space filling lesions, and offers an accurate means of demonstrating intracranial aneurysms, arteriovenous fistulas, and other arteriovenous anomalies.

SCHWEDEL

Castellanos, A., Pereiras, R., and Garcia, O.: Angiocardiography. Anatomo-Roentgenological Forms of the Transposition of the Great Vessels. Am. J. Roentgenol. **64**: 255 (Aug.), 1950.

The authors believe that there is no characteristic configuration in transposition of the great vessels. From seven angiocardiograms, three confirmed by autopsy, they conclude that the narrow vascular pedicle and a concave mid arch occur in some, but not in all, cases with this disorder. The characteristic feature of the angiocardiogram is the demonstration of simultaneous filling of the right chambers and the aortic arch. The left ventricle is usually poorly filled or not at all. The pulmonary artery may be filled if it arises from the right ventricle, but not if it originates in the left ventricle. The aortic arch may arise from the right side of the right ventricle or in the midline, and the resulting total vascular pedicle is narrow. In other instances, the ascending aorta curves to the left and forms a prominent upper convexity to the left. In still others, the ascending aorta arises on the left side of the right ventricle, forms a prominence on the left upper cardiac contour and then crosses the right main bronchus as if it were a right aortic arch. In such instances there may be

prominence of the vascular pedicle on the right as well as on the left.

SCHWEDEL

Miller, J. E.: Angiocardiography: The Prominent Pulmonary Artery Segment. Am. J. Roentgenol. **64:** (Aug.), 1950.

The author discusses lesions which stand out as a cause of prominence of the pulmonary artery segment. These are (1) idiopathic dilatation of the pulmonary artery, (2) pulmonary artery aneurysm, (3) patent ductus arteriosus, (4) interatrial septal defect, (5) Eisenmenger complex, and (6) poststenotic dilatation of the pulmonary artery. Prominence of the pulmonary artery in patent ductus arteriosus occurs in only slightly over 50 per cent of all cases, and hilar dance in less than 10 per cent. The aortic evagination sign is regarded as most important in the angiocardiogram, while reopacification of the pulmonary vessels is less frequent. Poststenotic dilatation is common in isolated pulmonary of infundibular stenosis.

SCHWEDEL

Lowenthal, M., and Brotherton, W.: A Device to Determine the Time of Exposure in the Heart of an Angiocardiogram. J. Lab. & Clin. Med. **36:** 319 (Aug.), 1950.

The phase of the cardiac cycle in which each exposure was made in angiocardiography was determined by means of a snap-action microswitch mounted on and activated by the "make" contact on the high tension contactor of the x-ray machine. The microswitch was arranged in such a manner as to close simultaneously with the high tension circuit which provided the voltage for the roentgen exposure. The standardization circuit of the electrocardiograph was utilized. The circuit consisted of a ource of voltage, usually a 1½ volt battery, a number of resistors, the galvanometer and a manually operated switch. By "shorting" the manually operated switch and connecting the microswitch in series with this circuit, the beginning of roentgen exposure was produced on the simultaneously recorded electrocardiogram. This was accomplished by the battery discharging across the galvanometer and causing it to deflect at the instant the high tension contactor closed. The time of the roentgen exposure was the upstroke of the "standardization deflection."

The advantages of the timing device are twofold, namely, its simplicity of application and the ability, when multiple exposures are used, to obtain roentgenograms in various phases of the cardiac cycle. This device can record but not control the time in the cardiac cycle at which an exposure is made.

MINTZ

Keele, K. D.: Angiocardiograms after Ligation of the Ductus Arteriosus. Brit. Heart J. **12:** 372 (Oct.), 1950.

The article presents angiocardiograms made before and after ligation of the ductus arteriosus in a girl 5 years old. Before ligation, a disc-like opacification of the origin of the left pulmonary artery is seen twice, once with opacification of the right ventricle and again with opacification of the aorta. The second opacification is not seen after ligation of the ductus arteriosus. The reappearance of the disc-like opacification of the pulmonary artery is regarded, therefore, as diagnostic of patency of the ductus arteriosus. Saucerlike dilatation of the aorta at the site of a patent ductus persists after ligation.

SOLOFF

SURGERY IN HEART AND VASCULAR SYSTEM

Lenègre, J., Brochen, G. G. and Lubin, J.: Appearance of a Continuous Murmur following Operative Anastomosis between Azygos and Pulmonary Vein in a Case of Mitral Stenosis. Arch. d. mal. du coeur **43:** 663 (July), 1950.

The authors describe the case of a 34 year old woman with typical mitral stenosis and repeated attacks of pulmonary edema. One such paroxysm occurred during cardiac catheterization and was accompanied by an increase in pulmonary pressure of more than 100 per cent. Since medical treatment proved unsuccessful, an anastomosis was performed between the right upper pulmonary vein and the azygos vein. The operation was followed by marked clinical improvement and by the appearance, in the second and third right anterior intercostal space, of a murmur which was musical in character and continuous, with presystolic and protodiastolic accentuation of intensity.

On the basis of their experience with 17 cases, in which a similar operation was performed (5 patients died, 5 showed improvement and 5 were unaffected) the authors recommend restricting the operation to cases without signs of right heart failure. Anticoagulants should be used postoperatively to prevent a closure of the anastomosis by thrombosis.

PICK

Pfeffer, K. H.: Disturbances of Circulatory Functions following Sympathectomy in Arteriosclerotic Hypertensive Patients. Ztschr. f. Kreislaufforsch. **39:** 465 (Aug.), 1950.

The author reports his observations on the result of thoracolumbar sympathectomy in 15 patients with long-standing hypertension and signs of progressive cerebral and renal arteriosclerosis. The effect of the operation upon blood pressure was unpredictable. Periods of sudden elevation of pressure, exceeding preoperative values and leading to apoplectiform attacks, changed abruptly to shock-like states with very severe hypotension. The majority of the patients died in such an accident within one year following surgery. The author recommends

caution in the performance of sympathectomy on older hypertensive patients with signs of progressive arteriosclerosis.

PICK

Brock, R. C., and Campbell, M.: Valvulotomy for Pulmonary Valvular Stenosis. Brit. Heart J. **12:** 377 (Oct.), 1950.

The authors report their clinical and operative experience in performing valvulotomies for relief of pulmonary valvular stenosis in 33 patients. Eighteen had pulmonary stenosis with a closed interventricular septum; in 15 the stenosis was thought to be part of Fallot's tetralogy. The mortality dropped from 50 per cent in the first 11 patients to 18 per cent in the last 22. The operation was considered dangerous in those over 20 years of age. The increasing safety of the operation in younger age groups suggests that it is indicated to relieve dangerously high right ventricular pressure. The greatest deterrent to successful operation is the danger of sudden death, due probably to coronary insufficiency. Any sudden deterioration of the patient during operation should lead to immediate division of the valve. In Fallot's tetralogy, the inability to demonstrate infundibular stenosis should lead to the suspicion of valvular stenosis. The pericardium should be opened to make a proper external examination of the heart.

SOLOFF

THROMBOEMBOLIC PHENOMENA

Wallerstein, R. S.: Thrombophlebitis Secondary to Acute Respiratory Infection. J. Mt. Sinai Hosp. 176 (Sept.–Oct.), 1950.

The sporadic occurrence of so-called idiopathic thrombophlebitis in young, ambulatory, presumably healthy individuals is discussed. Careful investigation in such instances has often elicited a history of an upper respiratory or grippe-like infection preceding the phlebitis by two or three weeks. In rare cases the phlebitis is recurrent, and these cases are believed by some authors to be a form of thromboangiitis obliterans limited to the veins. Three cases are reported, 2 in young healthy adults who developed acute thrombophlebitis of the deep leg veins two weeks following a grippe-like syndrome and responded well to dicumarol therapy. The third case, a 16 year old boy, had an acute thrombophlebitis of the right leg, associated with a pneumonia, with a later recurrence and the appearance of a second thrombophlebitis in the left leg.

CORTELL

VASCULAR DISEASE

Moia, B., and Albanese, A. R.: Arteriovenous Pulmonary Fistula. Rev. Argent. d. cardiol. **17:** 7 (May–June), 1950.

The authors report the case of a 27 year old woman who, since the age of 5, had exertional dyspnea, chest pain, headache, cyanosis and clubbing of the fingers. On physical examination, a slight decrease of the vesicular murmur at the right lung base was noted, while the heart seemed normal. The electrocardiogram showed right axis deviation. Fluoroscopy disclosed a triangular pulsating shadow at the right lung base, suggesting an arteriovenous fistula. The latter was confirmed by angiocardiography. There was a polycythemia of 5,700,000 with 17.79 Gm. hemoglobin. Oxygen saturation of the arterial blood was 69 per cent. Cardiac output, determined by Fick's method, was 6.7 liters per minute, 64 per cent of which was shunted via the fistula into the pulmonary veins.

Surgical resection of the middle right lobe was successfully performed. Cyanosis disappeared and the blood picture became normal on the sixth day. The patient was on the way to recovery but, on the fourteenth day, a few minutes after a pleural puncture, sudden death occurred. No autopsy is reported. The authors review 77 cases of arteriovenous pulmonary fistula reported in the literature.

LUISADA

Edwards, E. A.: Thromboangiitis Obliterans in Women. Possible Relation to Rheumatic Disease. New England J. Med. **243:** 290 (Aug.), 1950.

The author presents the case histories of 6 female patients in whom the clinical diagnosis of thromboangiitis obliterans occurred concomitantly with the diagnosis of rheumatoid arthritis, rheumatic fever, iridocychitis and/or erythema nodosa. He includes 2 additional patients, one male and one female, who showed rheumatoid arthritis and/or rheumatic fever with peripheral vascular disease, in whom the diagnosis of thromboangiitis obliterans had not been made.

The author postulates that angiitis of the peripheral vessels may be part of the collagen disturbance accompanying rheumatic states.

NADLER

Helmsworth, J. A., McGuire, J., and Felson, B.: Arteriography of the Aorta and its Branches by Means of the Polyethylene Catheter. Am. J. Roentgenol. **64:** 196 (Aug.), 1950.

The authors describe the technic of passing a polyethylene catheter into the brachial, ulnar collateral, or the femoral artery under roentgenoscopic control, the catheter being opacified with the contrast medium to be injected. The possibility of thrombosis was minimized by a stream of injected heparin.

Coronary artery visualization was successful in 5 dogs, but in only 2 of 6 patients. One of these patients died immediately after the last of five injections of radiopaque dye, and no cause for this sudden death was evident at autopsy. Aortography by the catheter route was successful in establishing the diagnosis in one instance of aortic thoracic aneurysm,

and in demonstrating aortic coarctation and arterial collaterals in a 10 year old child. Abdominal aortography demonstrated one instance each of abdominal aneurysm and aortic obstruction with collateral arterial supply. Other diagnoses made with the aid of this technic were aneurysm of the innominate artery, and details of arteriovenous communication. Cerebral angiography may also be performed with this technic. The rapid injection of large amounts of dye into the cerebral circulation might be averted by digital compression of the common carotid arteries.

SCHWEDEL

Kernwein, Graham A.: Management of Arteriosclerosis Obliterans in Cold Climates. Lancet **2:** 318 (Sept.), 1950.

The author calls attention to the prevalence of arteriosclerosis obliterans in 25 per cent of women and 55 per cent of men over 50. These subjects are unusually susceptible to frostbite. The underlying pathologic physiology is briefly outlined, as is the clinical syndrome and differential diagnosis. The author emphasizes the importance of prophylactic care in all over 50, laying special emphasis on warmth, the avoidance of injury and overexertion. Nonsurgical treatment is briefly reviewed. The author recommends novocaine block of the paravertebral sympathetic ganglia, particularly where functional obstruction is demonstrated, and he feels that some cases warrant sympathectomy.

TANDOWSKY

Seybold, W. D., and Musgrove, J. E.: Surgical Aspects of Mesenteric Vascular Occlusion. Proc. Staff Meet., Mayo Clin. **25:** 585 (Oct.), 1950.

In mesenteric vascular occlusion, abdominal pain is usually the first and foremost of the patient's complaints. It is usually severe and constant in character. Early in the attack the meager signs that are to be elicited on physical examination may be difficult to reconcile with the presence of a serious and urgent surgical lesion, but as ischemia or congestion of the bowel is succeeded by necrosis and frank gangrene, signs reflecting these changes and the accompanying changes in bowel function develop.

Although the mortality rate in mesenteric vascular occlusion has been very high in the past and will always remain high because of the serious lesions with which it is often associated, early laparotomy for resection of the involved bowel and mesentery in those patients whose general condition permits can be expected, nevertheless, to save most of the patients operated upon. Resection of the infarcted intestine and mesentery and a closed, aseptic primary anastomosis is the procedure of choice. The involvement of great lengths of the bowel should not deter the surgeon from completing the procedure if the general condition of the patient is reasonably good.

Of the 24 patients who form the basis of this report, 10 had resections and only 1 of the 10 died. The 11 who did not undergo exploration and the 3 who underwent simple exploration died.

SIMON

OTHER SUBJECTS

Wyss-Dunant, E.: Pulse Rate at High Altitudes. Schweiz. med. Wchnschr. **80:** 223 (March), 1950.

These observations concerning three groups of subjects were made during the Swiss Himalaya expedition in 1949. The pulse frequency of Europeans in the first group remained nearly constant up to an altitude of 7000 meters. Those in the second group manifested an increase of frequency with each increase in altitude and then showed a tendency to return to the original level. Subjects in the third group whose pulse frequency began to fall at relatively low altitudes (2000 to 3000 meters) did very poorly at high altitudes. Subjects in the first two groups can be considered "well adapted" to high altitudes. Compared to Europeans, the Sherpas (born at 4000 meters) had a higher pulse frequency at high altitudes. Their physical activity was also greater.

RITTER

Gover, M., and Pennell, M. Y.: Statistical Studies of Heart Disease. VII. Mortality from Eight Specific Forms of Heart Disease Among White Persons. Pub. Health Repts. **65:** 819 (June 30), 1950.

A study of vital statistics of heart disease in the United States shows that there is a higher mortality for men of all ages than for women in all categories except acute rheumatic fever. In general, mortality was higher in the northern than in the southern sections of the eastern United States. While recorded mortality tended to be higher in urban than in rural areas, such factors as accuracy of reporting may affect these statistics. In urban areas the excess of mortality rates of men over women with heart disease is greater than in rural areas. Mortality from myocardial disease was less than two-thirds as high in the South as in the North.

In persons from 5 to 35 years of age, valvular heart disease is the major cause of death from heart disease; in persons 35 to 65 years mortality from coronary artery disease is a large factor, being responsible for as much as 44 per cent among men. In persons over 65 years of age, myocardial diseases form the major portion of heart disease mortality and account for nearly two-thirds of cardiac deaths among women.

WAIFE

Padget, P., Webster, B., Densen, P. M., Nicol, C. S., and Rich, C. I.: Studies in Cardiovascular Syphilis. I. A Preliminary Report. Am. J. Syph., Gonor. & Ven. Dis. **34:** 319 (July), 1950.

The authors report a pilot study of the value of penicillin in the treatment of cardiovascular syphilis.

The histories of 1020 patients with clinical diagnoses of aortic regurgitation due to syphilis of the aorta, without saccular aneurysm and without general paresis, were analyzed. Preliminary statistical study indicated that retrospective analysis of the total materials available in clinic files could not provide the basis for evaluating the effectiveness of a method of treatment for syphilitic aortic regurgitation. The only sure way to get significant information would be to treat alternate patients, holding the others as controls. Since this would not be feasible in a chronic disease, the alternative would be to devise a system of matching cases which would allow valid comparisons. Such studies are under way and will be reported in the future.

SCHWARTZ

Barnett, C. W., and Small, A. A.: The Effect of Treatment on the Prognosis of Cardiovascular Syphilis. Am. J. Syph., Gonor. & Ven. Dis. **34:** 301 (July), 1950.

The authors have analyzed the outcome of treatment in 334 patients with aortic regurgitation or saccular aneurysm due to cardiovascular syphilis and present a detailed discussion of the statistical difficulties in evaluating the effect of anti-syphilitic therapy in cardiovascular syphilis.

It is concluded that there is a consistent diminution in the effectiveness of specific treatment as the disease advances. Therapy is of doubtful value after symptoms have appeared, but is definitely effective if there has also been a moderate amount of therapy before the onset. It is also effective when administered after cardiovascular disease has developed, but before it has advanced to the symptom-producing stage, and even more effective when given before the diagnosis has been established.

SCHWARTZ

Mills, M. D., and Smith, H. L.: Paroxysmal Tachycardia with Attacks of Unconsciousness. Minnesota Med. **33:** 703 (July), 1950.

The authors report the case history of a 21 year old patient who suffered from attacks of paroxysmal tachycardia, accompanied by syncope with prolonged unconsciousness. Nine attacks of unconsciousness with loss of memory of the event had occurred during a three year period. Tachycardia was consistently present at the time of the attacks. At no time had there been loss of sphincteric control, an aura, or an observed convulsive movement. On several occasions rapid heart action, characterized by a precipitous onset and sudden return to normal, had occurred without syncope.

The authors did not witness an attack of syncope, and physical examination was essentially normal. An electroencephalogram was essentially normal. An electrocardiogram showed a rate of 56, sinus arrhythmia with an occasional ventricular premature contraction, low amplitude QRS waves in leads I, II, and III, inverted T waves in leads III, V_1 and V_2, and positive T waves in lead V_5. The authors conclude that the clinical history and course were consistent with a diagnosis of paroxysmal tachycardia.

SCHWARTZ

Slobody, L. B., Rook, G. D., Leuberg, M., and Morcy, M.: Studies of the Cardiovascular and Renal Systems in the Newly Born Infant Using Fluorescein. Pediatrics **6:** 254 (Aug.), 1950.

Using alkalinized 5 per cent fluorescein solution, the umbilical-vein–to–lip circulation time was determined on 45 normal infants within one hundred and forty minutes after delivery. A polyethylene tube was placed in the umbilical vein of the cut umbilical cord, and an 18 or 19 gage needle on a tuberculin syringe containing the fluorescein was inserted into the proximal end of the tubing. Under ultraviolet light, the first appearance of fluorescein on the lips was considered the endpoint. The umbilical-vein–to–lip time ranged from 3.1 to 7.0 seconds with a mean circulation time of 4.8 $\pm$ 0.7 seconds. In a second group of 45 normal infants, the tube was advanced below the skin into the ductus venosus. The mean circulation time in these cases was 4.4 $\pm$ 0.6 seconds with a range of 3.3 to 5.8 seconds.

The authors offer this test as an aid in the differential diagnosis of the cause of cyanosis in the newborn.

MARGOLIES

Duncan, C. M., and Stevenson, I. P.: Paroxysmal Arrhythmias: A Psychosomatic Study. Geriatrics **5:** 259 (Sept.–Oct.), 1950.

Twenty-six unselected cases with supraventricular arrhythmias were studied for the possible etiologic factor of emotional stress. Thirteen had some degree of structural heart disease of various etiologies; in the remaining 13, there was no evidence of organic heart disease. Fifteen of the patients had paroxysmal auricular or nodal tachycardia, and the remaining 11, paroxysmal auricular fibrillation. Eighteen showed long standing and pronounced anxiety. Twenty had an unusual degree of hostility which was poorly expressed. In 19 some degree of compulsive behavior was displayed. Twenty had significant periods of depression. The episodes of arrhythmia occurred during certain emotional states of anxiety and resentment. In 2 patients, episodes of the paroxysmal arrhythmia were recorded during the interview while discussing pertinent personal problems. Ten of the patients had less frequent attacks following improvement of their emotional status.

The authors state that the occurrence of an arrhythmia is related to the product of the susceptibility of the heart, and to the stress to which it is subjected. Although there was increased susceptibility to emotional disturbances in the group with structural heart disease, the role of stress was still apparent in

those both with and without apparent organic heart disease. The authors emphasize the fact that therapy can consist of a modification of attitudes and emotional states, as well as of the indicated drug therapy.

MARGOLIES

Lottenbach, K., and Stucki, N.: The Delay of the Pulse Wave in Disturbances of the Peripheral Circulation. Cardiologia **17**: 7, 1950.

The authors studied the velocity of propagation of the peripheral pulse wave in 12 normal subjects and 10 patients with localized stenosis or occlusion of an artery of a lower extremity. For their investigations they used an apparatus which permits the registration of an electrocardiogram together with the oscillometric curve of an extremity. In normal circulation the main (physiologic) delay of the pulse wave of the lower extremity takes place in the segment between the heart and femoral artery, and is succeeded by an increase in velocity toward the periphery. In patients with peripheral vascular disease a delay of the pulse wave can also be observed below a peripheral point of obliteration, probably due to a decrease in tone of the arterial wall.

PICK

AMERICAN HEART ASSOCIATION, INC.

1775 BROADWAY, NEW YORK 19, N. Y.

Telephone Plaza 7-2045

RESEARCH GRANTS-IN-AID APPROVED

Forty-nine grants-in-aid to institutions for research studies have been approved by the Board of Directors on recommendation of the Research Committee of the Scientific Council. These awards are in addition to the Established Investigators and Research Fellows previously announced. An additional twenty applications have been approved and will be supported if funds are secured. Affiliated heart associations have been requested to consider supporting some of these.

The awards follow:

Continuing Grants-in-Aid

University of Georgia School of Medicine, Augusta, effects of the adrenolytic agents on the intact cardiovascular system of the anesthetized dog when administered in the presence of sympathomimetic agents, by *Raymond P. Ahlquist.*

Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, nature and cause of the vasoconstriction which appears in the course of perfusion of isolated organs, by *Harold D. Green.*

University of Tennessee College of Medicine, Memphis, development of methods for detection of altered pathways of blood flow through kidneys of intact dogs under various experimental conditions, by *C. Riley Houck.*

Tulane University of Louisiana School of Medicine, New Orleans, cytochemical and histochemical approaches to renal physiology, with particular reference to electrolyte reabsorption in congestive failure, by *Nathaniel B. Kurnick.*

Western Reserve University School of Medicine, Cleveland, myocardial metabolism, by *Victor Lorber.*

Tulane University of Louisiana School of Medicine, New Orleans, hemodynamic and iron storing function of ferritin, with particular reference to the kidney, by *H. S. Mayerson.*

Peter Bent Brigham Hospital, Boston, further development and use of the artificial kidney as a therapeutic and investigative tool in cardiovascular and renal disease, by *John P. Merrill.*

Cornell University Medical College, New York, relationship between increased activity of the adrenal cortex and posterior lobe of the pituitary gland and fluid and electrolyte retention in edema, by *Robert F. Pitts.*

Harold Brunn Institute for Cardiovascular Research, San Francisco, relationship of changes in plasma and tissue sodium to the development of 'shock' in myocardial infarction, by *John J. Sampson.*

Emory University School of Medicine, Atlanta, response of the pulmonary vascular bed to hemodynamic alterations in the systemic circulation by *James V. Warren.*

Albany Medical College, Union University, Albany, chronic physiologic aspects of atrial and ventricular septal defects; chronic physiologic aspects of mitral and aortic valvular insufficiency, by *Harold C. Wiggers.*

Committee on Anticoagulants of the American Heart Association. Chairman, Irving S. Wright.

New Grants-in-Aid

American Council on Rheumatic Fever, for cooperative research study of the relative effectiveness of ACTH and cortisone in the treatment of rheumatic fever and the prevention of rheumatic heart disease. Chairman, David D. Rutstein.

Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, immunophysiology of rheumatic fever, by *Jerry K. Aikawa.*

Harvard Medical School, Boston, fundamental hemodynamic aspects of chronic circulatory congestive failure, by *James K. Alexander.*

La Rabida Jackson Park Sanitarium, Chicago, mode of action of hyaluronidase in causing increased vascular permeability and the nature of its inhibition by adrenal steroids and other compounds, by *Earl P. Benditt.*

Western Reserve University School of Medicine, Cleveland, to study *in vivo* the microscopic changes in the circulating blood and the reactions of small blood vessels in patients with heart disease and thromboembolism receiving anticoagulant therapy, by *Edward H. Bloch.*

Temple University School of Medicine, Philadelphia, exploring the nature of endocarditis in dogs with arteriovenous fistulas as well as obtaining more information on factors influencing the susceptibility of dogs to this disease, by *J. Richard R. Bobb.*

Columbia University College of Physicians and Surgeons, New York, response of the splanchnic circulation to stress in normal and hypertensive human subjects with special reference to autonomous vascular adjustments, by *Stanley E. Bradley.*

Emory University School of Medicine, Atlanta, controlling factors in the renal maintenance of sodium balance, by *Walter H. Cargill.*

Cornell University Medical College, New York, effects of drugs on the action potential of heart muscle, by *McKeen Cattell.*

Fels Research Institute, Antioch College, Yellow Springs, for the use of the Fels oxygenator in experiments on hypothermia, congestive heart failure and neonatal asphyxia, by *Leland C. Clark and Frank Gollan.*

Pathological Institute, McGill University, Montreal, for studies tracing the fate of labelled cellular elements in atherosclerotic lesions in rabbits fed cholesterol, by *G. Lyman Duff.*

Ochsner Foundation Hospital, New Orleans, measurement of blood flow by recording changes in the electrical conductivity of various tissues, by *Thomas Findley.*

Mt. Sinai Hospital, New York, contribution of exercise to the genesis and perpetuation of congestive heart failure, by *Alfred P. Fishman.*

University of Colorado School of Medicine, Denver, etiology of rheumatic fever using tissue culture technics, by *Lloyd Florio.*

Harold Brunn Institute for Cardiovascular Research, San Francisco, metabolism of cholesterol, by *Meyer Friedman.*

University of British Columbia, Faculty of Medicine, Vancouver, B.C., the role of the adrenal gland and the kidney in the maintenance of "self-sustained hypertension" in the rat, by *Sydney M. Friedman.*

University of Minnesota Medical School, Minneapolis, etiologic and pathogenic mechanisms in rheumatic fever as revealed through studies of basic relationships of immunologic, endocrinologic, and biochemical events to pathologic processes related to those responsible for rheumatic disease, by *Robert A. Good.*

Yale University School of Medicine, New Haven, hemodynamic factors affecting electrolyte metabolism and the renal excretion of electrolytes; the effects of administered solutes on the formation of tissue fluid and the flow of lymph, by *Allan V. N. Goodyer.*

Children's Hospital, Boston, methods for grafting of blood vessels, by *Robert E. Gross.*

University of Pennsylvania School of Medicine, Philadelphia, biochemical pathways by which cholesterol and fat are synthesized and

metabolized in the body. The action of hormones upon the biosynthesis of cholesterol and lipids, by *Samuel Gurin*.

University of Texas Medical Branch, Galveston, the relationship of the adrenals, pituitary, kidneys and dietary constituents to the development and pathogenesis of parabiotic hypertension, by *Charles E. Hall*.

University of Utah College of Medicine, Salt Lake City, pharmacology, physiology, and biochemistry of the heart, by *Stewart C. Harvey*.

Presbyterian Hospital, Chicago, identification of the conduction system of the heart, by *George M. Hass*.

Yale University School of Medicine, New Haven, hypertension, cholesterol and arteriosclerosis, by *John H. Heller*.

Massachusetts General Hospital, Boston, factors that regulate extracellular fluid volume in the normal and edematous subject, by *Alexander Leaf*.

Columbia University College of Physicians and Surgeons, New York, revascularization of the heart, by *Ferdinand F. McAllister*.

Stritch School of Medicine, Loyola University, Chicago, for separation and identification of blood plasma proteins and other plasma components by ionography (electrophoresis on paper), by *Hugh J. McDonald*.

University of Michigan Medical School, Ann Arbor, cardiac metabolism, as related to epinephrine-induced arrhythmias and tachycardia, by *Mark Nickerson*.

Dartmouth Medical School, Hanover, N. H., further development and application of electrical impedence methods to the measurement of various cardiac and circulatory problems, by *Jan Nyboer*.

New York University-Bellevue Medical Center, New York, experimental studies on methods for the interruption of the cardiac and pulmonary circulations by refrigeration and with a new type of oxygenator, by *John J. Osborn*.

Yale University School of Medicine, New Haven, metabolic basis and treatment of heart failure, by *William T. Salter*.

Institute for Enzyme Research, Madison, oxidative enzymes of heart cyclophorase (mitochondrial preparation) and the effect of drugs and pathologic conditions on the energy-yielding reactions, by *D. Rao Sanadi*.

State University of New York Medical Center at Syracuse, New York, for the study of the nervous control of water and electrolyte excretion by the normal kidney, by *Otto W. Sartorius*.

Mt. Sinai Hospital, New York, evaluation of the role of the kidney in the pathogenesis of heart failure, by *Jonas H. Sirota*.

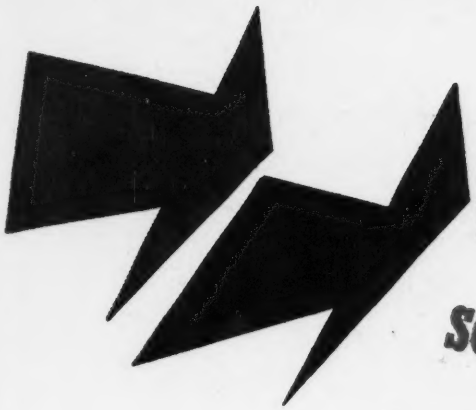
Southwestern Medical School of the University of Texas, Dallas, steroids and sodium in relation to hypertension. Steroids in relation to toxemia of pregnancy. Serum emulsifying forces in relation to atherosclerosis, by *Louis Tobian, Jr.*

Marine Biological Laboratory, Woods Hole, Mass., molecular mechanism of muscular contraction, by *Albert Szent-Gyorgyi*.

Harvard Medical School, Boston, relationship of the adrenal to hypertension, by *George W. Thorn*.

ARTERIOSCLEROSIS SOCIETY

The American Society for the Study of Arteriosclerosis will hold its 1951 annual meeting on November 5 and 6 at the Hotel Knickerbocker in Chicago. Abstracts will be received until June 1. Dr. Nelson W. Barker, Mayo Clinic, Rochester, Minn., is Program Chairman.



water follows sodium
sodium follows

MERCUHYDRIN®

SODIUM

effective, well tolerated...
a diuretic of choice

"Reaser and Burch, using radioactive isotopes, have confirmed earlier evidence that mercurial diuretics greatly increase the urinary loss of sodium. The sodium diuresis precedes water diuresis by two to four hours, and sodium excretion per day may be increased sevenfold while water excretion is merely doubled."

Editorial: J.A.M.A. *135*:576, Nov. 1, 1947.

"... The concentration of sodium in the urine was increased nearly two and one-half times by the injection of the mercurial diuretic, while the average total excretion of sodium in 24 hours was increased more than four times by MERCUHYDRIN injections."

Griggs, D. E., and Johns, V. J.: California Med. *69*:133, Aug. 1948.

MERCUHYDRIN Sodium (brand of meralluride sodium) is available in 1 cc. and 2 cc. ampuls.

Lakeside Laboratories, INC., MILWAUKEE 1, WISCONSIN

Circulation

APRIL, 1951
VOL. III NO. 4

The JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS